ECONOMIST IMPACT

Rare paediatric neurological diseases: A focus on Europe

COMMISSIONED BY PTC THERAPEUTICS

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About this report

Rare paediatric neurological diseases: A focus on Europe is an Economist Impact report (formerly the EIU), supported by PTC Therapeutics, a biopharmaceutical company. This independent research explores two rare neurological disease groups in children—lysosomal storage disorders (LSDs) and neurotransmitter diseases —focusing on the patient and family experience in Europe, as well as challenges for healthcare professionals and opportunities for policymakers. This report focuses on these two disease groups, as they run a chronic course and place sustained personal, social and economic burdens on patients and their families.

Reviewing evidence in the literature, collecting data, and interviewing representatives of clinical practice and patient organisations were undertaken to inform this report. Our thanks are due to the following for their time and insights (listed alphabetically):

- **Michelle Bottomley**, principal genetic counsellor, Manchester Centre for Genomic Medicine, Manchester University NHS Foundation Trust, UK
- **Professor Tim Cox**, professor of medicine emeritus and director of research, University of Cambridge; honorary consultant physician in metabolic medicine, Addenbrooke's Hospital, Cambridge, UK; lead patron, MLD (Metachromatic Leukodystrophy) Support Association UK; and an advisor to several charities including Metabolic Support, The UK Gauchers Association and The Cure & Action for Tay-Sachs Foundation
- **Dorica Dan**, chair, Romanian Prader Willi Association; co-ordinator, the NoRo Center; president, the Romanian National Alliance for Rare Diseases; chair, the Romanian Association for Rare Cancers; member, EURORDIS Board of Officers and Board of Directors; and mother of a daughter with Prader-Willi Syndrome
- **Shagufta Khan**, senior genetic counsellor, The West Midlands Clinical Genetics Department, Birmingham Women's and Children's NHS Foundation Trust, UK
- **Toni Mathieson**, chief executive, Niemann-Pick UK; UK representative, the International Niemann-Pick Disease Alliance; trustee, the International Niemann-Pick Disease Registry; chair, the UK LSD Patient Collaborative. She has lost three children to Niemann-Pick Disease Type C
- **Tobias Mentzel**, chairman, European Leukodystrophy Germany (ELA Deutschland e.V.). He has a son who is living with leukodystrophy

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- **Puri Ríos Aroca**, president, De Neu, Asociación de Enfermedades de los Neurotransmisores (Association of Neurotransmitter Diseases), Spain. She has a daughter living with a neurotransmitter disease
- **Professor Maurizio Scarpa**, director, the Regional Co-ordinating Center for Rare Diseases, Udine University Hospital, Udine, Italy; co-ordinator, the European Reference Network for Hereditary Metabolic Diseases (MetabERN); professor of paediatrics, the University of Padova, Italy

This report was researched by Elizabeth Sukkar and Ingrid Torjesen of Economist Impact, formerly the Economist Intelligence Unit. The findings and views expressed in this report are those of Economist Impact and do not necessarily reflect the views of the sponsor.

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Executive summary

Rare paediatric neurological conditions are debilitating diseases with massive impacts on the day-to-day lives of children and their families. Most rare diseases have neurological symptoms, and about 90% of those affecting children have major neurological effects impacting ability to achieve key cognitive and physical development milestones.

This report highlights the difficulties in achieving a timely and accurate diagnosis as well as the numerous challenges to providing adequate care and support. It concludes that policymakers should work to develop a rare diseases healthcare ecosystem that is sufficiently resourced and organised to enable even the most complex conditions to be assessed and managed expeditiously. Ultimately, policymakers should aim to leave no-one behind. Healthcare professionals will play an important role, for which education will be critical, as well as ensuring patients are referred to centres of excellence better able to provide quality care.

This report focuses on two disease groups—LSDs and neurotransmitter disorders—for two reasons. First, these diseases run a chronic course and therefore place sustained personal, social and economic burdens on patients and their families. Second, with advances in molecular genetics and cell biology, the underlying cause can be identified and allow the disease mechanism to be addressed in a manner that may improve clinical management and care.

These disorders are caused by disruptions to biological pathways, which can impact multiple organs and systems and therefore cause diverse clinical manifestations and symptoms, requiring multidisciplinary care. Although rare individually, there are numerous types of these disorders. They are frequently inherited as a recessive trait, meaning families need genetic counselling. Treatment, where available, is focused on mending disrupted pathways or alleviating the effects of their disruption.

To highlight policy priorities for improving care, patient outcomes and quality of life, Economist Impact embarked on a project to better understand what impact these disorders have on patients and their families.

Research findings include:

- **Diagnosis remains a major challenge in Europe**: both sets of conditions are difficult to diagnose. As they share symptoms with more

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common conditions, this leads to delays in achieving an accurate diagnosis. While there are efforts in Europe to address the need for educating medical professionals around these conditions, the average time from the first symptom to diagnosis is at least three to five years at best, experts told us. For the best outcomes in preventing lifelong disabilities, some of these disorders require treatment from birth or the first few months of life. Lack of a definitive diagnosis is also a stressor for families and carers. Even where there is no treatment available, a diagnosis enables families to understand the condition, access wider supportive care and gain advice from other families in the same position.

- **Access to newborn screening and genetic testing varies considerably in Europe**: the provision of neonatal screening, which can identify neurological conditions at birth, varies dramatically between European countries. Italy is seen as the "champion", screening for over 40 conditions, while others, like the UK and Romania (nine and four, respectively), screen for fewer conditions. Screening raises complex ethical, practical and economic considerations that healthcare systems must grapple with. While the cost of genetic testing has fallen, some families still face hurdles accessing testing and genetic counselling. Analysing genetic data is complicated and time consuming and there is a shortage of analysts of genetic data and genetic counsellors across Europe.
- **Access to multidisciplinary care is essential**: patient care needs to be co-ordinated and managed through specialist centres, with some care delivered locally. Many of these conditions are ultra-rare, meaning there may only be a handful of patients with a specific condition in Europe and few specialists experienced in managing them. Specialist centres have started collaborating to provide the best care and outcomes for patients through European Reference Networks (ERNs) by developing standardised protocols and holding multidisciplinary virtual panels to review patients. While ERNs are a major step in the right direction, aspects of their work still need improvement.
- **Access to innovative therapies is a challenge in some countries:** advanced therapies for rare diseases may see delays in adoption or not be funded at all. Some patients may need to travel abroad to access new therapies because their home country lacks specialised centres, which, due to their very nature, are not established in all countries. European countries are also evolving a variable approach to how advanced therapies for rare diseases are considered for reimbursement. Although there are mechanisms to support cross-border healthcare in Europe, the process is not well known or easy to use. An effective EU cross-border healthcare framework is critical to enable patient access to advanced therapies for severe and rare genetic diseases.
- **Registries of patients are essential tools for research in understanding the disease and developing new treatments**: these provide data on patterns of genetic mutations and symptoms, natural disease progression, delivery of care and treatment outcomes, including long-term safety and effectiveness. They can also help connect patients with investigators that are setting up clinical trials for innovative therapies. The scope of current registries is limited, as they are based around the place and type of treatment, and there are limited comprehensive national or Europe-wide registries.
- **Patient and family support is crucial**: healthcare systems and healthcare

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professionals try their best to support patients and families living with these conditions, but outside of the family, much of the burden lies with rare disease patient groups. The amount of care required means that at least one parent usually gives up work to care for the child full time, which has a psychological impact and can affect finances. Relationships and marriages can face pressures, and siblings are also affected. Rare disease patient groups do fill some care and support gaps, including information on services, schools, home adaptions, social care and benefits. They also help families to negotiate the system, but are limited in number and not sufficiently well resourced.

Policy takeaways

The report's conclusion highlights the key areas for consideration by policymakers and healthcare providers to improve care (see "Conclusion and policy takeaways"). These are focused around ensuring prompt diagnosis and effective management. In summary:


Neonatal screening for a wider range of conditions


Standardised neonatal screening policies embedded within national health systems


More genetic counsellors and greater access to them


Further training for all doctors on rare conditions


Improved access to, and collaboration between, specialist centres


Comprehensive and interoperable registries needed


A more user-friendly cross-border healthcare framework


Funding models taking more account of the unique nature of rare diseases


Improve the quality of life and wellbeing of the child and family


Care pathways need to acknowledge these situations and encourage greater provision


Patient groups need more support, as they act as linchpins for families and carers

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Chapter 1: Burden around rare paediatric neurological conditions: a focus on lysosomal storage disorders and neurotransmitter diseases

Patients living with all types of rare diseases face two common major challenges—a lack of timely and accurate diagnosis and difficulties accessing effective treatment. Rare paediatric neurological conditions are no different.

The average time for a diagnosis from the first symptom is at least three to five years at best, says Maurizio Scarpa, director of the Regional Co-ordinating Center for Rare Diseases at Udine University Hospital in Italy and professor of paediatrics at the University of Padova. "It can be decades; it depends on the disease."

The burden of rare diseases

While rare diseases have, by definition, a low prevalence, the total number of people affected is significant.

A disease affecting fewer than 5 people in 10,000 is considered rare in the EU. While that might seem small, it means around 246,000 people across the EU as a whole are affected.[1] There are around 5,000-8,000 distinct rare diseases in total, together affecting 6-8% of the EU population, that is between 27 million and 36 million people.[2]

Research by Orphanet, a European initiative to improve the diagnosis, care and treatment of patients with rare diseases, found that 71.9% of rare diseases are genetic and 69.9% begin in childhood.[3]

The majority of rare diseases have neurological manifestations,[4,5] and around 90% of those affecting children have major neurological effects.[6]

It is difficult to specify the exact number of rare neurological diseases, as this depends on the criteria and sensitivity of the classification system. New diseases continue to be identified. At the moment, about 7,000 rare diseases have been identified, says Professor Scarpa, who is also the co-ordinator of the European Reference Network for Hereditary Metabolic Diseases (MetabERN), an EU project that connects centres of clinical excellence. (See "Specialist

[1] https://ec.europa.eu/health/non_communicable_diseases/rare_diseases_en Accessed September 14th 2021

[2] Ibid

[3] Nguengang Wakap S, Lambert D M, Olry A, et al, "Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database", *European Journal of Human Genetics*, 28, 165–173 (2020)

[4] Reinhard C, Bachoud-Lévi AC, Bäumer T, et al, "The European Reference Network for Rare Neurological Diseases", *Front Neurol*, 2021 Jan 14;11:616569

[5] Federico A, "Rare Neurologic Diseases and Neurological Sciences: a report for the celebration of the 2020 Rare Diseases Day", *Neurol Sci*, 2020 Mar;41(3):491-495, doi: 10.1007/s10072-020-04287-8, PMID: 32062737

[6] https://www.ninds.nih.gov/Current-Research/Research-Funded-NINDS/Translational-Research/urgent-network Accessed September 14th 2021

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"Usually, a rare disease is only suspected after a battery of tests and the exclusion of other common diseases, so these children and their parents do not have an easy life; they undergo quite a lot of tests and most of the time receive a wrong diagnosis and wrong therapies."

Maurizio Scarpa, director of the Regional Coordinating Center for Rare Diseases, Udine University Hospital, Udine, Italy, and coordinator of the European Reference Network for Hereditary Metabolic Diseases (MetabERN)

care through European Reference Networks" in Chapter 2.) The Orphanet classification system lists almost 50 rare neurological disorders (See Appendix 1).[7] Some of these diseases develop in the first year of life, some in the first decade and others even later. "It is not easier to get a diagnosis if the child has symptoms in the first year, rather than in the third decade, because these are not diseases with a specific symptom that raises immediate suspicion of a particular disease," explains Professor Scarpa.

Rare neurological diseases generally do not have pronounced symptoms and often affect multiple organs and systems, meaning families can be referred from specialist to specialist when looking for answers.

"The diagnosis of a rare disease is not easy," adds Professor Scarpa. "So, usually, a rare disease is only suspected after a battery of tests and the exclusion of other common diseases, so these children and their parents do not have an easy life; they undergo quite a lot of tests and most of the time receive a wrong diagnosis and wrong therapies," he says.

Others have looked at the policy dimensions around rare diseases, such as EURORDIS' Rare2030 work.[8] To better understand the patient and family experience and policy environment around rare paediatric neurological diseases, this report will focus on two disease groups where there has been some development in clinical research around advanced therapies:

- **LSDs** are due to lysosomal dysfunction. Lysosomes are membrane-enclosed structures that contain enzymes capable of breaking large molecules (such as proteins and lipids) into smaller ones so that they can be recycled by the cell. Lysosome dysfunction occurs when the synthesis of lysosomal enzymes and lysosomal membrane proteins is disrupted, which can result in cellular damage. For most of these conditions, the main clinical effects are neurological in origin and associated with progressive morbidity.[9]
- **Neurotransmitter diseases** are due to disruption of the synthesis, degradation or transport of one or more neurotransmitters, which are an essential part of the central and peripheral nervous system responsible for relaying commands and receiving sensory signals.

While rare individually, there are numerous types of these disorders. (See Table 1 and Appendix 2 for a full description.)

[7] https://www.orpha.net/consor/cgi-bin//Disease_Classif.php?lng=EN&data_id=181&PatId=13024&search=Disease_Classif_Simple&new=1 Accessed September 14th 2021

[8] http://www.rare2030.eu/ A(accessed on November 17th 2021)

[9] Edelmann MJ and Maegawa GHB, CNS-Targeting Therapies for Lysosomal Storage Diseases: Current Advances and Challenges, *Front. Mol. Biosci.*, 2020, 7:559804, doi: 10.3389/fmolb.2020.559804

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Shagufta Khan, senior genetic counsellor at the West Midlands Clinical Genetics Department in the UK's Birmingham Women's and Children's NHS Foundation Trust, says these two types of disorders go "hand in hand" because they both occur due to disruptions to biological pathways, either in communication (neurotransmitter disorders) or metabolism (LSDs).

"They're both very rare types of conditions that we're seeing more often now, because we're getting better at diagnosing them, and as a result we're learning more about them," she says.

"They're both types of conditions that if diagnosed early enough could, in some cases, have a treatable outcome," she says. "Now we're learning more about the conditions, there's the possibility of finding more treatment options, including novel therapies such as cell and gene therapies. The possibilities could be endless."

Table 1: Examples of the neurotransmitter diseases and lysosomal storage disorders

Neurotransmitter diseases:

- Biogenic amines neurotransmitter disorders
- BH4 deficiencies
- Cerebral folate deficiencies
- Serine deficiencies
- Disorders of glycine metabolism
- GABA related disorders
- Co-Chaperone deficiencies

[Source: iNTD]

Lysosomal storage disorders:

- Aspartylglucosaminuria
- Batten Disease
- Cystinosis
- Fabry disease
- Gaucher disease types I,II,III.
- Glycogen storage disease II (Pompe disease)
- GM2-Gangliosidosis Type I (Tay-Sachs disease)
- GM2-Gangliosidosis Type II (Sandhoff disease)
- Metachromatic Leukodystrophy
- Mucolipidosis Types I, II/III and IV
- Mucopolysaccharide Storage Diseases
- Niemann-Pick Disease Types A/B, C1 and C2
- Schindler Disease Types I and II

[Source: NORD]

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"Losing skills is a feature of many neurodegenerative disorders, in fact, it's almost a definition. They lose speech, they lose movement, they lose the ability to swallow, and they lose sensation."

Tim Cox, professor of medicine emeritus and director of research at the University of Cambridge; honorary consultant physician in metabolic medicine at Addenbrooke's Hospital, Cambridge, UK

Care and support needs of patients and families

Caring for a child living with a rare neurological disorder varies enormously according to the disease's progression and onset, the family's financial situation, and their ability to access healthcare services and gain support from their wider personal network.

These children quickly need rapidly increasing care, says Tobias Mentzel, chairman of European Leukodystrophy Germany, who has a son with leukodystrophy.

The impact on families can be "brutal", says Professor Tim Cox, an academic physician who conducts research at the University of Cambridge and cares for patients with rare diseases at Addenbrooke's Hospital in Cambridge, the UK.

If the child is expected to die in infancy, this is always on parents' minds, but with juvenile and adult forms of these conditions, parents watch as their child gets angrier and more frustrated as the condition worsens.

"That's torture to watch. Mum and dad are older and finding it harder to cope, there's pressure on the other children, and it breaks up relationships and marriages," says Professor Cox. "Losing skills is a feature of many neurodegenerative disorders, in fact, it's almost a definition," he says. "They lose speech, they lose movement, they lose the ability to swallow, and they lose sensation."

Most children old enough to attend early years education, such as kindergarten/nursery or school, then drop out and have to be cared for at home full-time, meaning that parents rearrange their lives. "Your child is losing abilities, which is tough to see, so there's that psychological burden. If both parents are working, at least one will need to quit their job, sometimes both," says Mr Mentzel.

For example, most individuals with the neurotransmitter disorder aromatic L-amino acid decarboxylase (AADC) deficiency will require life-long care, and around 71% will be entirely reliant on their caregiver. These caregivers report needing to provide continual supervision and administration of medication, frequent hospital visits which leaves them unable to leave the house, maintain employment, and disrupts their sleep.[10]

Usually, the mother quits employment to look after the child. As well as putting aside career aspirations, this kind of care creates a heavy physical and psychological burden. Parents can often neglect their own healthcare and social needs, developing depressive symptoms and feelings of isolation.[11,12] Psychological support

[10] Skrobanski H, Williams K, Werner C, O'Neill S, Buesch K, Acaster S. The impact of caring for an individual with aromatic l-amino acid decarboxylase (AADC) deficiency: a qualitative study and the development of a conceptual model. Curr Med Res Opin. 2021 Oct;37(10):1821-1828. doi: 10.1080/03007995.2021.1955668. Epub 2021 Aug 1. PMID: 34259573. https://doi.org/10.1080/03007995.2021.1955668

[11] Sestini S, Paneghetti L, Lampe C et al, "Social and medical needs of rare metabolic patients: results from a MetabERN survey", *Orphanet J Rare Dis,* 16, 336 (2021), https://doi.org/10.1186/s13023-021-01948-5

[12] Cardinali P, Migliorini L, Rania N, "The caregiving experiences of fathers and mothers of children with rare diseases in Italy: challenges and social support perceptions", *Front Psychol*, 2019;10(1780)

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is available to only 29% of parents and carers of patients living with rare metabolic disorders, despite 70% believing such support is necessary, a survey found.[13]

The survey, published by MetabERN in 2021, is believed to be the only specific study of the care and social requirements of patients with a rare inherited metabolic disease in Europe, and like studies conducted on patients with other rare diseases, found a widespread lack of social, psychological, and economic support for patients.

A total of 924 patients and caregivers completed the survey, with Spain, Italy and Germany being the most represented, while around half of the respondents were children. Around 29% of the patients had LSDs and 2% had neurotransmitter disorders.

In most cases, costs for medical devices, medicines, food supplements, physiotherapy and speech therapy are funded to some extent by the national health system but 20-28% of respondents were not aware of whether medical devices, physiotherapy or speech therapy are covered, and 36% and 45% of respondents, respectively, did not know whether they were entitled to psychological or home care assistance. No coverage for psychological assistance for patients was reported by 21%, while 36% said it was available, with 66% thinking it was needed.

The levels of practical care and supportive therapy available for these children varies across Europe, with Eastern European countries not having sufficient specialised care services, particularly for rehabilitation and palliative care, says Dorica Dan, chair of the Romanian Prader Willi Association.

A Spanish study published in 2021, which looked at the experience of caregivers (of children) and patients with rare diseases, found that they do not feel that they receive sufficient support to manage their condition.[14]

"Even in Germany, which provides higher levels of support, families are hit financially due to the fact that parents may have to give up work and may have additional costs, for example, in adapting their home," says Mr Mentzel.

Finding the right school and opportunities for children to interact with others can also be difficult.

The MetabERN survey found that around half of children with these disorders were in school. Two-thirds (65.5%) attended regular state schools, 16% state-funded special schools and 9.4% private institutions.[15]

Other types of services, such as a home tutors, day care centres, psychomotor skills development and vocational training programmes are available for a limited number of patients, but around half of the respondents do not know about these services.[16]

"Finding a suitable school for your child's abilities is complex," says Puri Ríos Aroca, president of the patient group De Neu (Association of Neurotransmitter Diseases in Spain) and a

[13] Sestini S, Paneghetti L, Lampe C et al, "Social and medical needs of rare metabolic patients: results from a MetabERN survey", *Orphanet J Rare Dis,* 16, 336 (2021), https://doi.org/10.1186/s13023-021-01948-5

[14] Guilabert M, Martínez-García A, Sala-González M, Solas O, Mira JJ,. "Results of a Patient Reported Experience Measure (PREM) to measure the rare disease patients and caregivers experience: a Spanish cross-sectional study", *Orphanet J Rare Dis,* 2021 Feb 5;16(1):67, doi: 10.1186/s13023-021-01700-z, PMID: 33546736; PMCID: PMC7866674

[15] Sestini S, Paneghetti L, Lampe C et al, "Social and medical needs of rare metabolic patients: results from a MetabERN survey", *Orphanet J Rare Dis*, 16, 336 (2021), https://doi.org/10.1186/s13023-021-01948-5

[16] Ibid

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parent to a child living with a neurotransmitter condition. Her daughter was moved from her first primary school because she was not receiving the support she needed, but the current school has worked well, as teachers have been very involved and supportive. Ms Ríos Aroca remarks that "there are very few schools in Spain where there is real inclusion. We had to visit several schools and spoke to them about this disease."

At secondary school level, children are more likely to attend special schools, because as they become older the differences with their friends are more noticeable. "They start caring about other kinds of things, so the gap has increased, so next year we will be moving our daughter to a special college," Ms Ríos Aroca explains.

Opportunities for children to play are also important. Ms Ríos Aroca is creating another patient association in Valencia, where she lives, to facilitate play between children that have similar disabilities.

Lack of access to respite care services to give parents and families of children with neurological disorders a break is also a major issue. This is something emphasised by Toni Mathieson, chief executive of Niemann-Pick UK, who also acts as the UK representative for the International Niemann-Pick Disease Alliance. She had three children who died of Niemann-Pick Disease Type C.

Above all, these families face a future full of uncertainties. They may not know what condition the child has, how it will affect them and by how much their life course will be curtailed. For example, children with Niemann-Pick disease can live for a few years or decades. Those with type A rarely live beyond four years, those with type B generally live much longer and with type C there's "huge variability", says Ms Mathieson, who is also chair of the UK LSD Patient Collaborative.

"Parents are often told to take their child away and make memories because life expectancy is short, and then that child is still with them when they're 14, because we can't predict, what's going to happen. We have so many different mutations, and two siblings who have the same mutations can have completely different experiences of a condition," she says.

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Chapter 2: Approaches to improving the lives of patients and their families and carers

Diagnosis is the gateway to care

For some rare neurological disorders with an effective treatment, such as neurotransmitter disorders related to serine or dopamine deficiency,[17,18] and Pompe disease,[19] which is an LSD, prompt treatment can have a dramatic impact on reducing complications and the need for lifelong care. This requires diagnosis, ideally at birth or during pregnancy.

The impact of early therapy can be life-changing for some of these conditions, as highlighted by the experience of De Neu, which supports 15 families with children living with neurotransmitter diseases in Spain. "We have some children with a dopamine defect and if you give them dopamine early in life, they can lead a more satisfactory life," says Ms Ríos Aroca. "We have another child in the group with a disorder related to serine deficiency. Serine is very important in very early development. If serine is given while the mother is pregnant, then the outcome is very good for the child. This child was not diagnosed until he was at least six months old and he is now being treated with serine; he can walk more or less but he cannot speak. He is 14 right now."

One of the key symptoms of Pompe disease is a deteriorating liver. "If we could give the enzyme replacement treatment earlier on, we could actually save that liver and not have to have a liver transplant," says Ms Khan.

Even when there is no effective treatment for the condition, diagnosis helps, as it opens up access to a team of specialists. "While they might not be able to cure or slow the disease, they will at least be able to help with symptom control. It will also open up access to practical and social support through patient organisations," says Ms Mathieson.

It also means families can learn more about the condition and talk with other families that have a child with the same disease. This allows families to share experiences and gain advice on how to deal with particular symptoms, says Ms Ríos Aroca.

[17] van der Crabben S N, Verhoeven-Duif N M, Brilstra E H et al, "An update on serine deficiency disorders", *J Inherit Metab Dis*, 36, 613–619 (2013), https://doi.org/10.1007/s10545-013-9592-4

[18] https://rarediseases.org/rare-diseases/sepiapterin-reductase-deficiency/ Accessed September 30th 2021

[19] https://rarediseases.org/rare-diseases/pompe-disease/ Accessed September 30th 2021

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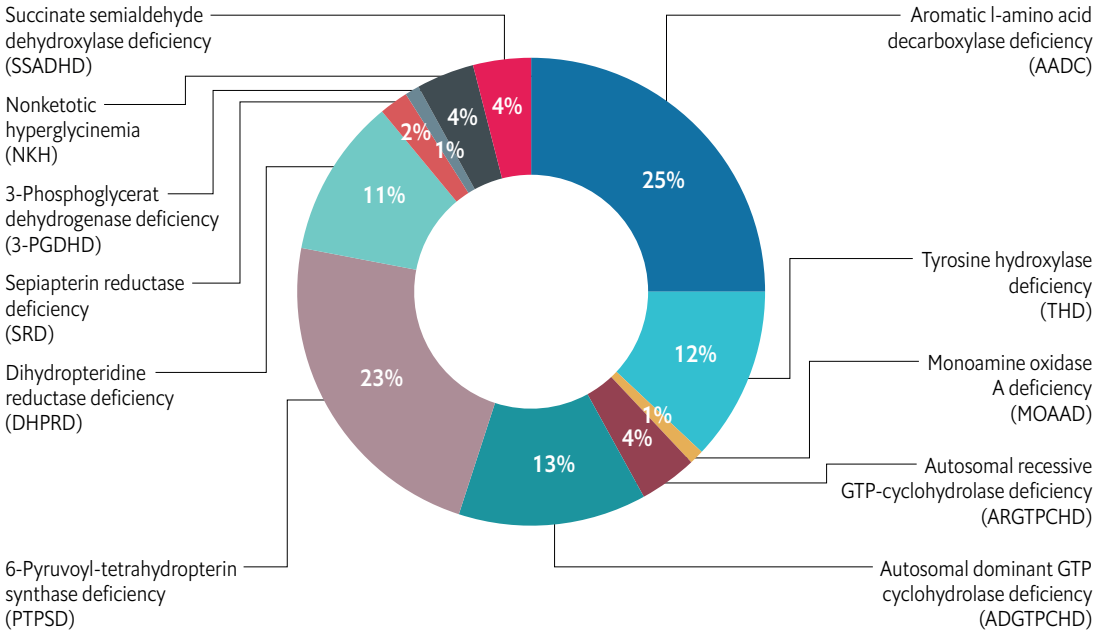
But a diagnosis of rare neurological disorders is a challenge. For example, a study looking at neurotransmitter diseases found the age range at first symptoms for AADC deficiency was one to five months (median age: 2.5 months), while the age range at diagnosis was 4.9 to 32 years (median 9.8 months) (See Figures 1 and 2).[20]

Figure 1: Neurotransmitter deficiencies revealed in an international patient registry (iNTD) by frequency and distribution

As of September 2021, there are 41 participating centres (in 20 countries) and 497 registered patients (448 are active patients) in the iNTD. By boosting understanding around these diseases, looking at the patient's quality of life and diagnostic and therapeutic strategies, the INTD hopes to develop consensus care guidelines. The graph below looks at the latest publicly available data on the specific neurotransmitter deficiencies of the patients in the registry from a study published in 2016.



Sources: https://www.intd-registry.org/; Opladen T, Cortès-Saladelafont E, Mastrangelo M, et al. The International Working Group on Neurotransmitter related Disorders (iNTD): A worldwide research project focused on primary and secondary neurotransmitter disorders. Mol Genet Metab Rep. 2016;9:61-66. Published 2016 Oct 20. doi:10.1016/j.ymgmr.2016.09.006

[20] Opladen T, Cortès-Saladelafont E, Mastrangelo M, et al, "The International Working Group on Neurotransmitter related Disorders (iNTD): A worldwide research project focused on primary and secondary neurotransmitter disorders", *Mol Genet Metab Rep, 2016;9:61-66, October 20th 2016, doi:10.1016/j.ymgmr.2016.09.006*

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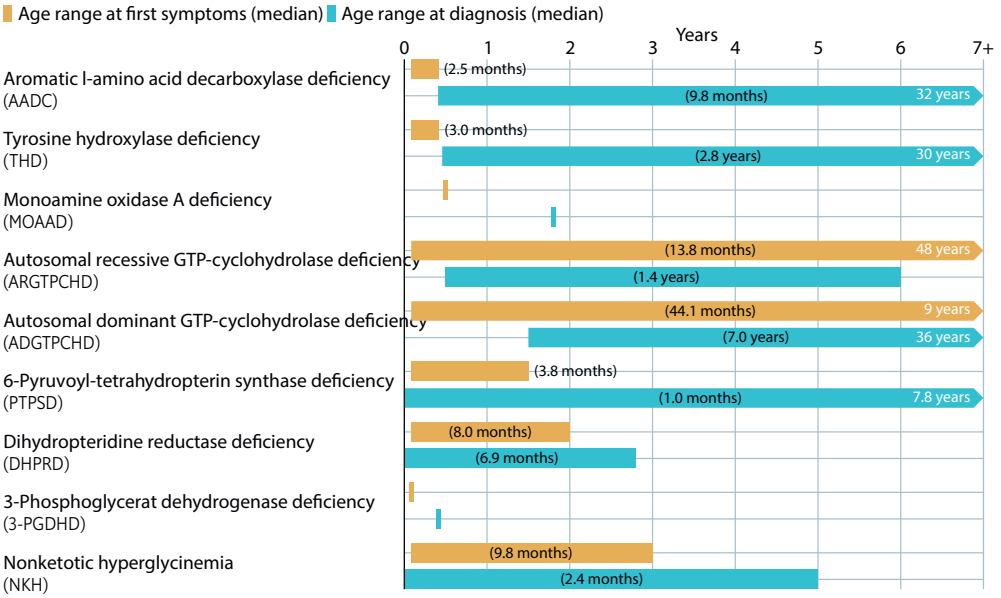
Figure 2: Neurotransmitter diseases: age at first symptoms and age at diagnosis
(for selected diseases in the iNTD registry)



Source: Opladen T, Cortès-Saladelafont E, Mastrangelo M et al. The International Working Group on Neurotransmitter related Disorders (iNTD): A worldwide research project focused on primary and secondary neurotransmitter disorders. Mol Genet Metab Rep. 2016;9:61-66. Published 2016 Oct 20. doi:10.1016/j.ymgmr.2016.09.006 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5094101/

Diagnosis takes so long because these disorders are so rare: unless there is a family history, these disorders would not be thought about. Such disorders have a diverse range of symptoms, which frequently occur in more common conditions, so these need to be ruled out first.

The speed of diagnosis very much depends on the behaviour of the individual doctor that sees the child initially, and in turn the behaviour of the specialists that they are then referred on to, Mr Mentzel says, as well as the ability of families to negotiate the system.

It is important for doctors to give time and attention to finding out what is wrong, otherwise the patient will not be diagnosed, there will be a delay or even worse they will be misdiagnosed, says Ms Ríos Aroca. Her daughter lives with succinic semialdehyde dehydrogenase (SSADH) but her initial symptoms were originally suspected to be due to low oxygen levels after she fell and lost consciousness.

It is very difficult for clinicians to quickly understand what kind of disease a patient is presenting with, i.e. that it is a rare neurological disorder rather than a common condition, and it is "unrealistic" to expect all doctors to recognise individual rare diseases because there are too many, Mr Mentzel concedes. But he adds that "they need to have a good understanding [of] what to do with patients where they have no clue what condition they have."

"It is often the mother or the grandmother who picks up [that] something is wrong," says Professor Cox. Most conditions are autosomal recessive, and although it is rare for a close relative to have the same condition, it may have been seen in the wider family or close geographic or religious community where there is enhanced

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awareness due to a high level of consanguinity (descended from the same ancestor). For example, Tay-Sachs disease, Gaucher disease and Niemann-Pick type A are more prevalent in Ashkenazi Jews.[21]

The speed of diagnosis is much better when signs of a potential neurodegenerative condition are picked up in infants, as services for adolescents and young adults are much less organised.

The paediatric world is very familiar with the difficulties around these conditions, as each individual disease is a rarity while a primary care physician may never have seen them before.

But, in general, many neurodegenerative diseases have a common pattern of disability that requires the same diagnostic skill set; this can be brought to bear quite quickly once the referral is made to the appropriate specialist, Professor Cox says.

Genetic testing plays an important role in identifying the underlying disease mechanism

Even with advances in and expansion of genetic testing, many patients with rare neurological diseases remain undiagnosed. "That's a huge problem, because they don't know what they have to do and where to look for support," says Ms Dan, who has a daughter living with Prader-Willi Syndrome, which is caused by missing genetic material in chromosome number 15 and can usually be confirmed by genetic testing.[22]

Rare neurological disorders comprise more than 1,700 distinct genetic disease entities, but rates of molecular genetic diagnoses have been stuck at about 30-50% across next-generation sequencing to determine the RNA and DNA genetic variation associated with rare neurological disease phenotypes.[23]

Professor Cox says: "Once there's some recognition that something is wrong, and when the decision-making and reporting system is properly attuned to the technology, whole exome sequencing may come up with a diagnosis for as many as 40% of children within a year or two."

As understanding of the genetic determinants of diseases continues to grow, repeat systematic re-analysis of genetic data held on patients with unknown conditions could provide more diagnoses. In one recent study re-analysis of genetic data held on patients with undiagnosed conditions provided diagnoses for up to 29% of these patients.[24] Indeed, the term "syndromes without a name" (SWAN) is used when children have symptoms of a genetic disorder, but these symptoms can't be diagnosed. Around 6,000 children are born with SWAN each year in the UK alone.[25]

Some patients are diagnosed based on the clinical signs and symptoms, but it is always best to confirm that diagnosis by genetic testing where an appropriate test is available.

While some patients miss out on treatment and care because they have not been diagnosed, others are misdiagnosed. "If you're receiving a treatment that is actually meant for another condition, and your mechanism of disease is completely different, it's not going to help and it could make things worse. We have seen that in a number of patients," says Ms Mathieson.

[21] Zlotogora J, Patrinos G P & Meiner V, "Ashkenazi Jewish genomic variants: integrating data from the Israeli National Genetic Database and gnomAD", *Genet Med* 20, 867–871 (2018), https://doi.org/10.1038/gim.2017.193

[22] https://www.nhs.uk/conditions/prader-willi-syndrome/ Accessed October 7th 2021

[23] Schüle R, Timmann D, Erasmus C E et al, "Solving unsolved rare neurological diseases—a Solve-RD viewpoint", *Eur J Hum Genet*, 29, 1332–1336 (2021), https://doi.org/10.1038/s41431-021-00901-1

[24] Ibid

[25] https://www.undiagnosed.org.uk/ Accessed October 7th 2021

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Genetic testing can be a long, drawn-out process. While genetic testing is becoming more available in many countries as the price of genome sequencing has fallen, not all tests are available in all countries meaning some samples have to be sent abroad, meaning a long wait for the results.

But genetic testing can be a long, drawn-out process. While genetic testing is becoming more available in many countries as the price of genome sequencing has fallen, not all tests are available in all countries meaning some samples have to be sent abroad, meaning a long wait for the results.

"For Niemann-Pick Disease Type C, for instance, you often wait three or four months for that test to come back. That's not quick enough when we're dealing with a neurodegenerative condition," says Ms Mathieson.

Despite living in the UK—a country considered at the forefront of genetic research[26,27] —Ms Mathieson's family's tests had to go abroad. "When we were diagnosed as a family, our tests had to go to France," she says. "That wouldn't happen now, but that still happens in many other countries."

And identifying a clear genetic cause is not as straightforward as most people think.

Everyone is a carrier of different recessive conditions, and even using whole genome sequencing it is not possible to make an immediate diagnosis for a single disease, says Professor Scarpa.

Our genomes are astonishingly diverse and polymorphic. Neurological disorders can involve disruptions of single or multiple genes, and even when there is only a single genetic locus implicated, interpreting the results of DNA analysis in a manner that is clinically appropriate and responsible is "quite a skill", Professor Cox explains.

Increasingly, whole genome sequencing is being used, which includes not only coding sequences (exons), but also non-coding (intronic) and regulatory sequences, as well as mitochondrial DNA.

"Depending on the particular region of DNA and complexity of the mutational landscape, a highly proficient professional may spend half a day or more to scrutinise the sequences related to a given gene," Professor Cox reveals.

A major problem is a shortage of people trained in bioinformatics who can analyse the data from genetic tests and make sense of them.[28] As Professor Scarpa explains, "new tools for analysis of molecular tests need to be created so that one day we can have a genetic test for everything for just a few Euros."

Europe's variations on neonatal screening

Screening at birth or during pregnancy allows children with inherited neurological diseases to be identified before symptoms appear. Children with certain conditions can be treated,

[26] https://www.gov.uk/government/news/human-genome-uk-to-become-world-number-1-in-dna-testing Accessed October 1st 2021

[27] https://www.england.nhs.uk/genomics/ Accessed October 7th 2021

[28] https://www.researchandmarkets.com/reports/5359636/bioinformatics-services-market-by-type?utm_source=GNOM&utm_medium=PressRelease&utm_code=mpm86r&utm_campaign=1563346+-+The+Worldwide+Bioinformatics+Services+Industry+is+Expected+to+Reach+%245.3+Billion+by+2026+at+a+CAGR+of+15.8%25+from+2021&utm_exec=jamu273prd Accessed October 8th 2021

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"I would like to see the UK's newborn screening panel expanded to contain more lysosomal storage disorders, such as Hurler's and Pompe's disease, as there are treatment options for children living with these conditions. For example, by detecting Pompe disease early enough we can prevent the need for liver transplants."

Shagufta Khan, senior genetic counsellor, The West Midlands Clinical Genetics Department, Birmingham Women's and Children's NHS Foundation Trust, UK

for example, with a special diet or enzyme replacement therapy to prevent or reduce the development and progression of symptoms.

"If we're able to identify and treat these serious conditions, where there is a treatment at an early stage, we save a lot of time and money, and dramatically improve children's lives in the process," says Ms Mathieson.

Ms Khan says: "I would like to see the UK's newborn screening panel expanded to contain more lysosomal storage disorders, such as Hurler's and Pompe's disease, as there are treatment options for children living with these conditions. For example, by detecting Pompe disease early enough we can prevent the need for liver transplants."

Currently, most countries only screen for paediatric neurological conditions if there is a specific therapy available to treat patients, says Mr Mentzel, and as our understanding of these conditions grows and new therapies come online, many countries are slow to update their screening panels, with most only updating them every five to ten years.

The addition of tests for certain diseases to these panels is also hindered in some countries, including Germany, by the fact that there will be no effective treatment available for some disorders or that some children may only ever experience mild symptoms, he explains. So, an argument against newborn testing is if the patients and their family are aware of a diagnosis of a degenerative condition from birth that will likely present later life or only mildly, then that "steals a few happy years away".

"This fact sometimes feels more critical than helping others who can benefit from newborn screening. Our perspective is that everyone who would like to know if they have a specific disease, even if it cannot be treated, should know because you avoid the 'diagnostic odyssey'," Mr Mentzel says.

Niemann-Pick Type C is an example of a condition with symptoms that may not show until someone is 40 or 50 years old. Overall, the benefits of knowing that a patient has a condition that may result in symptoms in later life outweigh the drawbacks, Ms Mathieson says, because symptoms can be watched for and acted on immediately.

"Whether a treatment exists or not, early diagnosis is the key to unlocking expert care and support services and informs reproductive choices," she says, adding that Niemann-Pick UK has supported several families that have had three or four children affected by the condition because they were unaware that the condition was affecting their family.

The International Society for Neonatal Screening (ISNS) says that the considerable variation in the practice of neonatal screening among the countries of Europe,[29] partly reflects differences in populations and resources, but also represents

[29] https://www.isns-neoscreening.org/supporting-the-development-of-newborn-screening-in-europe/ Accessed October 1st 2021

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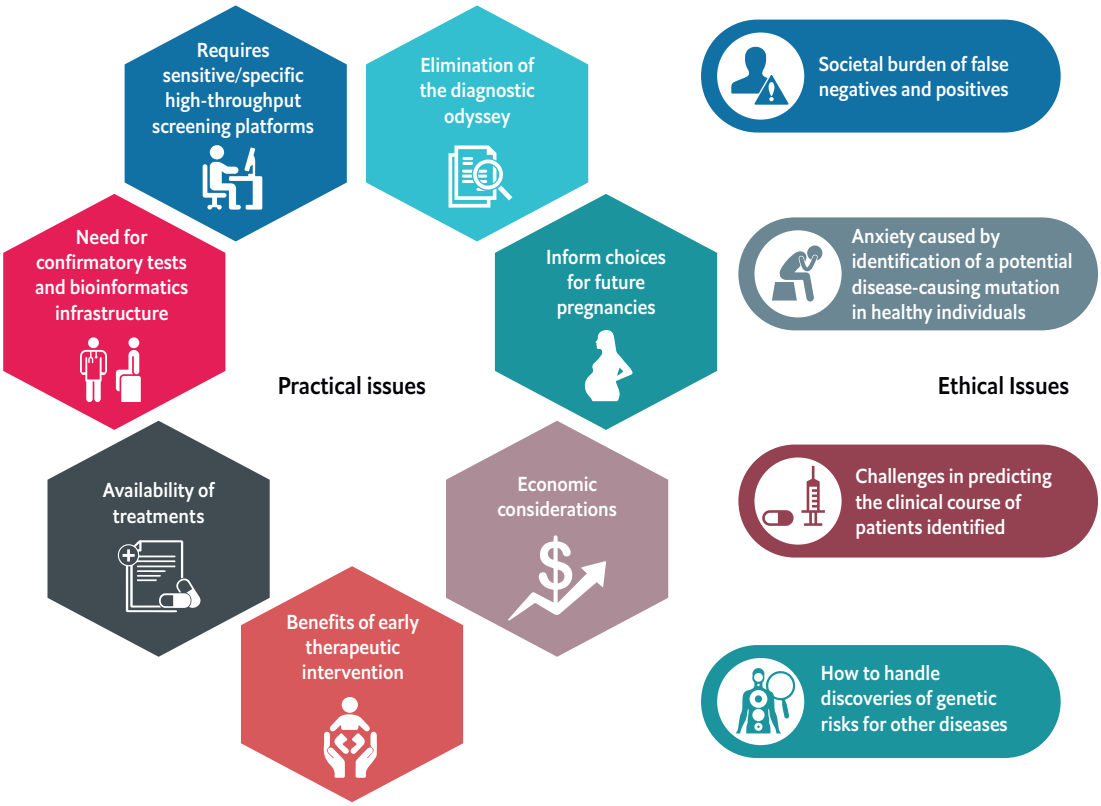
the differing decisions of national policymakers about the benefits and harms of screening (Figures, 3, 4 and 5, and Table 2). There are many practical and ethical issues to consider around screening. The ISNS, working with EURORDIS, an alliance of 970 rare disease patient organisations in Europe, is pushing for a more harmonised European approach to neonatal screening. EURORDIS is campaigning for Italian newborn screening to be endorsed as best practice and replicated across Europe.[30]

Figure 3: Factors that influence the introduction of newborn screening into practice



Source: Adapted from Platt, F. Emptying the stores: lysosomal diseases and therapeutic strategies. Nat Rev Drug Discov 17, 133–150 (2018). https://doi.org/10.1038/nrd.2017.214

While neonatal screening programmes have traditionally aimed to identify infants with treatable conditions, where early identification helps avoid irreversible damage, EURORDIS argues that screening should be considered for a wider range of actionable conditions that have other benefits for patients and parents. These include conditions where:

[30] EURORDIS, "Harmonised Newborn Screening in Europe - a window of opportunity that we should not miss!", October 13th 2021, https://www.eurordis.org/news/harmonised-newborn-screening-europe-window-opportunity-we-should-not-miss

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- early interventions lead to health gain for the newborn
- early diagnosis avoids the diagnostic odyssey
- parents will have reproductive options during subsequent pregnancies[31]

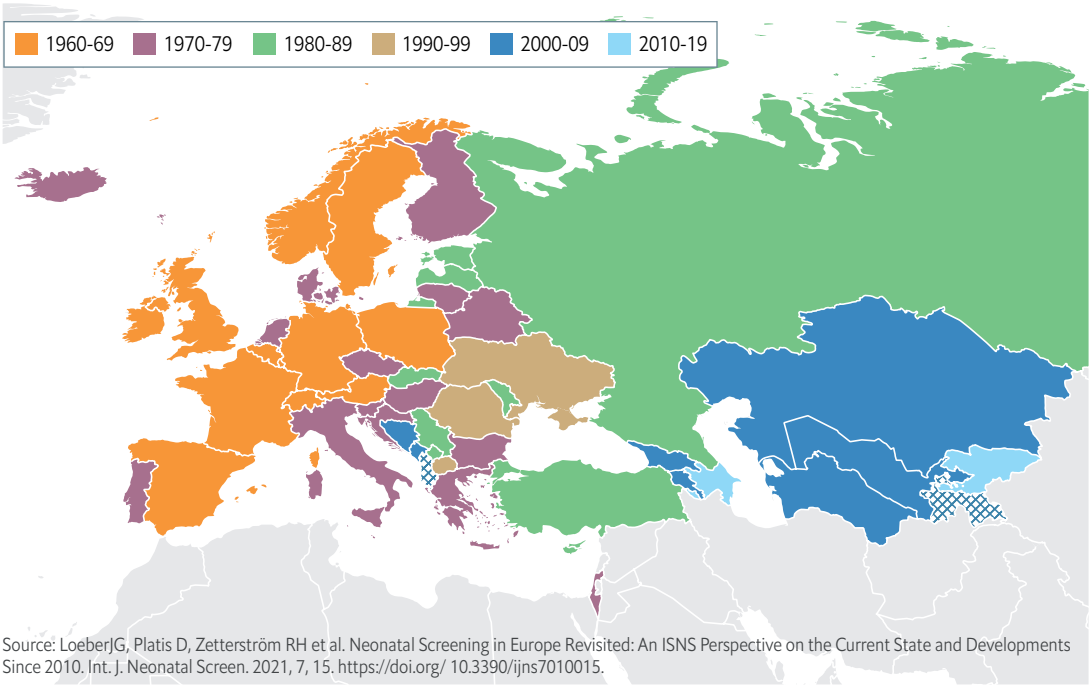
EURORDIS says that neonatal screening should be embedded in the national healthcare system and that European-wide standards for processes are needed.[32]

In Europe, Italy is considered the leader on neonatal screening (see box). "In Italy, newborn screening for over 40 diseases is mandatory according to the Law 167/2016," Professor Scarpa says. "Most of these conditions attack the central nervous system."

A recently launched European research project called Screen4Care is using genetic newborn screening alongside advanced analysis methods such as machine learning in an attempt to significantly shorten the time required for rare disease diagnosis. The five-year project involves a public-private consortium of 35 partners across 14 countries and is funded by the Innovative Medicines Initiative, a joint venture of the EU and the European Federation of Pharmaceutical Industries and Associations.[33]

Figure 4: Neonatal (newborn) blood screening starting year in Europe

Based on the International Society for Neonatal Screening's European region. Neonatal blood screening was introduced to Western Europe in the 1960s, and has expanded to Eastern countries over the next 40 years. Albania and Tajikistan (blue-hatched white on the map) have no neonatal screening programmes, although there is some activity in some Albanian hospitals.



Source: LoeberJG, Platis D, Zetterström RH et al. Neonatal Screening in Europe Revisited: An ISNS Perspective on the Current State and Developments Since 2010. Int. J. Neonatal Screen. 2021, 7, 15. https://doi.org/ 10.3390/ijns7010015.

[31] EURORDIS, "Key principles for newborn screening", January 2021, https://www.isns-neoscreening.org/wp-content/uploads/2021/01/eurordis_nbs_position_paper.pdf

[32] Ibid

[33] https://screen4care.eu/ Accessed November 2nd 2021

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Table 2: Country data and number of newborn diseases screened in Europe (conditions identified by screening using neonatal blood samples)

Country	Population (million)	Approx. number of infants	Number of conditions in screening anel + number of conditions in a pilot/regional screening
Albania (no screening)	3.0	36,000	no data
Armenia	3.1	36,000	2
Austria	8.8	87,000	26
Azerbaijan	9.7	170,000	5
Belarus	9.8	108,000	2
Belgium	10.5	117,000	17 + 3
Bosnia-Herzegovina	3.3	28,000	2
Bulgaria	7.4	61,000	3
Croatia	4.2	36,200	8
Cyprus	1.1	9500	2
Czech Republic	10.6	113,000	18
Denmark	5.6	63,000	19 + 1
Estonia	1.3	13,500	19
Finland	5.5	45,000	21 + 1
France	67	760,000	6
Georgia	3.7	48,500	3
Germany	80	787,000	17 + 2
Greece	10.5	80,000	4
Hungary	10	90,000	26 + 1
Iceland	0.35	4500	27 + 1
Ireland	4.9	59,700	8
Israel	9.2	194,000	19 + 1
Italy	60.5	434,000	31 + 4
Kazakhstan	18.7	402,000	2 + 1
Kosovo	1.8	25,000	no data
Kyrgyzstan	7.0	160,000	1

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Table 2 (continued): Country data and number of newborn diseases screened in Europe (conditions identified by screening using neonatal blood samples)

Country	Population (million)	Approx. number of infants	Number of conditions in screening anel + number of conditions in a pilot/regional screening
Latvia	1.9	20,800	6
Lithuania	2.8	24,600	4
Luxembourg	0.6	7200	5
Malta	0.48	4400	3
Moldova	3.5	37,400	1
Montenegro	0.62	7200	2
Netherlands	17.8	168,500	20 + 2
North Macedonia	2.1	20,000	25 + 1
Norway	5.3	55,500	23
Poland	38.4	373,000	27 + 2
Portugal	10.3	87,300	24
Romania	19.6	185,600	4
Russia	142	1,670,000	6
Serbia	7.0	65,000	3
Slovakia	5.4	57,000	25 + 2
Slovenia	2.07	20,000	19 + 1
Spain	46.5	372,000	7 + 26
Sweden	10	116,000	25
Switzerland	8.1	88,000	10
Tajikistan (no screening)	9.4	291,000	no data
Turkey	84.3	1,300,000	5
Turkmenistan	6.0	110,200	6
United Kingdom	66.6	760,000	9
Ukraine	43.7	393,000	4 + 24
Uzbekistan	31.3	760,600	2 + 19

Source: LoeberJG, Platis D, Zetterström RH et al. Neonatal Screening in Europe Revisited: An ISNS Perspective on the Current State and Developments Since 2010. Int. J. Neonatal Screen. 2021, 7, 15. https://doi.org/ 10.3390/ijns7010015

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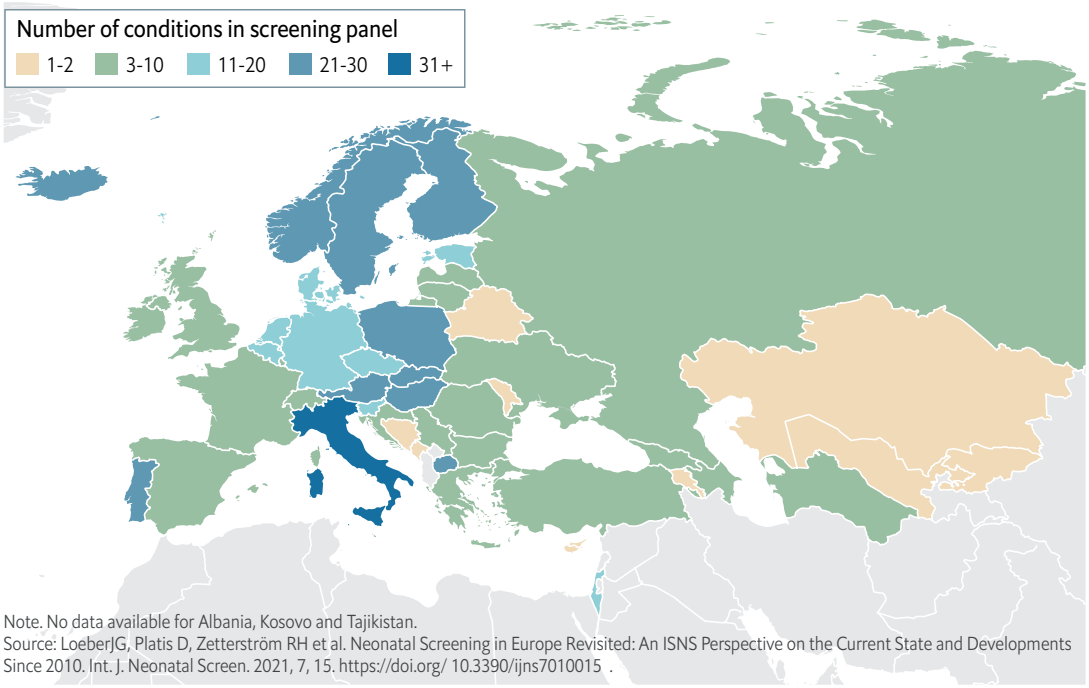
Figure 5: Neonatal blood screening in Europe

The number of conditions screened varies widely across Europe with no relation to GNP. Italy has been called the "champion" of NBS as it screens for more than 40 conditions. Other countries that screen for more than 20 diseases include Austria, Finland, Hungary, Iceland, North Macedonia and Poland, but many screen for fewer diseases such as France (six) and the UK (nine).



Note. No data available for Albania, Kosovo and Tajikistan.
Source: LoeberJG, Platis D, Zetterström RH et al. Neonatal Screening in Europe Revisited: An ISNS Perspective on the Current State and Developments Since 2010. Int. J. Neonatal Screen. 2021, 7, 15. https://doi.org/ 10.3390/ijns7010015 .

Neonatal screening has been mandatory in Italy for phenylketonuria, congenital hypothyroidism, and cystic fibrosis since 1992,[34] and in 2016 it was extended to 40 conditions.[35] The screening panel is now reviewed every two years, and the additional conditions added since have included LSDs.[36] Research is being undertaken for potential newborn screening for AADC deficiency, as clinical symptoms overlap with other conditions, often leading to delayed diagnosis.[37] New advanced therapies, such as cell and gene therapy, have emphasised the need for an early diagnosis.

The Italian constitution enshrined in law the right to health as a fundamental right of the individual and as a collective interest,[38] and this has encouraged health promotion and screening activities in Italy, says Professor Scarpa.

The conditions included are predominantly those with some form of treatment or a dietary intervention that could prevent or slow symptoms, he explains.

[34] Burlina A B, Corsello G, "Survey of Italian pediatricians' perspectives and knowledge about neonatal screening", *Italian Journal of Pediatrics, 2015 May;41:41, DOI: 10.1186/s13052-015-0147-1, PMID: 26021374, PMCID: PMC4462014*

[35] la Marca G, "La organización del cribado neonatal en Italia: comparación con Europa y el resto del mundo [The Newborn Screening Program in Italy: Comparison with Europe and other Countries]", Rev Esp Salud Publica, 2021 Jan 26;95:e202101007, Spanish, PMID: 33496274

[36] https://www.emjreviews.com/reproductive-health/article/newborn-screening-now-and-in-the-future/ Accessed October 1st 2021

[37] Brennenstuhl H, Kohlmüller D, Gramer G, et al, "High throughput newborn screening for aromatic L-amino-acid decarboxylase deficiency by analysis of concentrations of 3-O-methyldopa from dried blood spots", *J Inherit Metab Dis*, 2020; 43: 602– 610, https://doi.org/10.1002/jimd.12208

[38] Constitution of the Italian Republic, 1947, https://www.senato.it/documenti/repository/istituzione/costituzione_inglese.pdf

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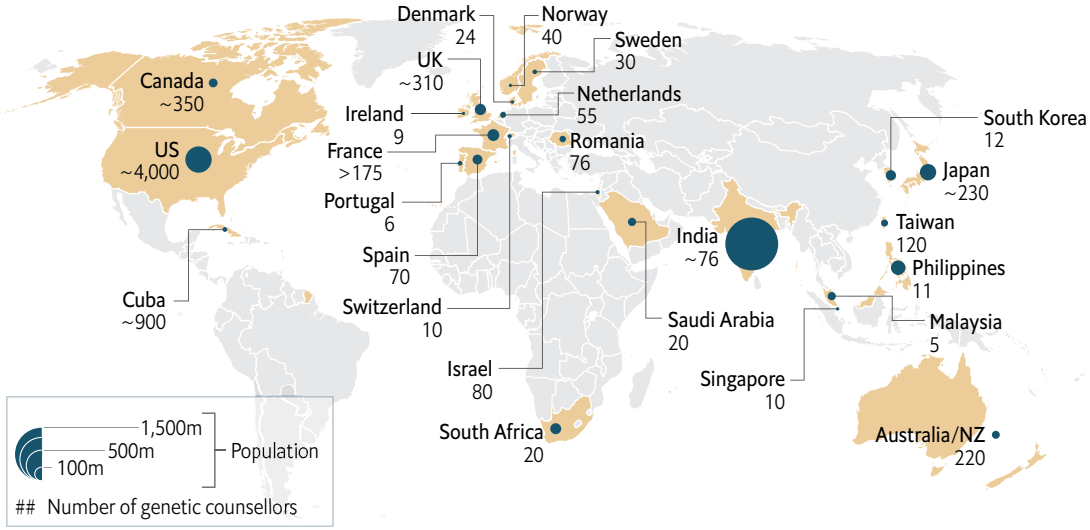
Genetic counselling supports the wider family

As well as a shortage of people with the skills to analyse genetic data to reach a diagnosis, there is also a shortage of genetic counsellors across Europe, although the profession is developing (Figure 6).[39,40] Genetic counsellors work with the immediate family of a child to help them understand the disease pathway, and what to expect in the future so they are better prepared. They also explain the potential repercussions for other family members in terms of their risk of being a carrier of the disorder and the potential for them to have a child with it, and the testing and support services available to them.

Ms Khan says: "We touch a little bit on the diagnosis, but go more into the genetic cause of the diagnosis and what it means for the family, and how parents are carriers and how we need to confirm this through blood samples. We discuss what it means for them for future pregnancies, and other children they may already have. We also talk about the wider family and talk about cascade screening for other siblings and the potential of them being carriers."

Figure 6: Estimated number of genetic counsellors globally

There are an estimated 7,000 genetic counsellors in 28 countries. In Europe, the profession is developing in more than 11 countries. In the UK, GCs are qualified to work autonomously or as part of a multidisciplinary care team. As genomics advances across the healthcare sector, their role will evolve. Not all countries in Europe have a certification or registration body.



Source: Abacan M, Alsubaie L, Barlow-Stewart K et al. The Global State of the Genetic Counseling Profession. Eur J Hum Genet 27, 183–197 (2019). https://doi.org/10.1038/s41431-018-0252-.

[39] Abacan M, Alsubaie L, Barlow-Stewart K et al, "The Global State of the Genetic Counseling Profession", *Eur J Hum Genet, 27, 183–197 (2019), https://doi.org/10.1038/s41431-018-0252-x*

[40] Ormond K E, Laurino M Y, Barlow-Stewart K et al, *"Genetic counseling globally: Where are we now?", Am J Med Genet Part C Semin Med Genet,* 2018; 178C: 98–107, https://doi.org/10.1002/ajmg.c.31607

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"We say to families that there is a slightly higher risk if they marry within the family, but there are many patients who are completely unrelated."

The chances of other couples in the wider family having a child with the same disorder will be really low, but genetic counsellors will seek to determine whether there was an increased risk because of geographical or cultural marriage practices, points out Michelle Bottomley, principal genetic counsellor, Manchester Centre for Genomic Medicine, Manchester University NHS Foundation Trust, UK.

Genetic counsellors say it is important to provide the right balance in counselling so people do not feel somehow to blame if they are in a consanguineous relationship. "It's a very delicate balance because it will be why both partners had a higher chance of being carriers, but it isn't the cause. At the end of the day, it can happen to any couple," Ms Bottomley says.

Where there is little evidence of a consanguineous relationship, often screening is only available to immediate family members, says Ms Mathieson. "When a child is diagnosed, then they might be offered testing for siblings, and usually parents because that helps with confirmatory testing, but outside of that there is nothing to support the wider family; that could be siblings of the parents who might be thinking about having children or might already have children and be worried about them having this disease."

"Often what happens is that they go to their GP for referral to genetic services, and they're told 'oh, it's far too rare, you don't really need testing, just carry on'." But Ms Mathieson says that's not good enough. "In some cases, it stops people from going on to have children because they're so worried because they've seen the impact of these conditions on their wider family."

Co-ordination of care and specialist centres

As neurotransmitter diseases and LSDs are incredibly rare, care needs to be co-ordinated through specialist centres, and as these disorders affect multiple organ systems, patients also need the care of multidisciplinary teams.[41,42,43]

"These are very complex diseases that cannot be followed by a single doctor," says Professor Scarpa. "Every rare disease needs to be followed by a specialist centre with a multidisciplinary team and an expert who is like an orchestra director."

Specialist medication is usually prescribed through a specialist centre initially, so patients may need to attend for check-ups and monitoring to make sure the therapy is working for them, says Ms Mathieson. If it does then they can be transferred to homecare with less frequent monitoring.

There are many countries and situations in which patients are treated and followed up only by specialist centres, which are not local to where they live, says Professor Scarpa. Patients and their families face quite a lot of expenses, including travel costs, that they need to sustain privately, so there is a need to boost home treatment, which is not uniform across Europe or even within countries. "We need to have better involvement of local hospitals, paediatric doctors

[41] *Ward C D, Phillips M, Smith A et al, "Multidisciplinary approaches in progressive neurological disease: can we do better?", Journal of Neurology, Neurosurgery & Psychiatry, 2003;74:iv8-iv12*

[42] Wassenberg T, Molero-Luis M, Jeltsch K et al, "Consensus guideline for the diagnosis and treatment of aromatic l-amino acid decarboxylase (AADC) deficiency", *Orphanet J Rare Dis*, 12, 12 (2017), https://doi.org/10.1186/s13023-016-0522-z

[43] Geberhiwot T, Moro A, Dardis A et al, "Consensus clinical management guidelines for Niemann-Pick disease type C", *Orphanet J Rare Dis*, 13, 50 (2018), https://doi.org/10.1186/s13023-018-0785-7

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and general practitioners [GPs]," says Professor Scarpa.

A UK study, published in 2021, found that uncoordinated care has a detrimental impact on people living with rare diseases and their carers.[44] Impacts include:

- physical health (including fatigue)
- financial (including loss of earnings and travel costs)
- psychosocial (including disrupting school, work and emotional burden)

The study highlighted the importance of flexible care by having support from a professional to co-ordinate care, changing the approach of clinics/appointments (where they take place, which services are available and how they are scheduled), and improving communication using technology, care plans, accessible points of contact and multi-disciplinary teams.

The MetabERN study of patients with a rare inherited metabolic disease in Europe found that most patients lacked access to specialised, disorder-specific medical services (61.1%) or emergency services specialised in their disease (72.3%) in their area.[45] However two-thirds (66.5%) reported that their country had a dedicated clinical pathway for their disorder, and almost 70% said they had easy access to their metabolic consultant/specialist or a member of their team.

Some countries are better served with specialist centres than others, and as many of these disorders are ultra rare, even teams in countries well served with specialist centres may have little experience in treating a specific condition.

"We should have specialised care services in each country," says Ms Dan. "But when the disease is so rare that it affects a small number of patients, we probably need a European centre to try to develop knowledge and expertise."

That is where ERNs come in.

Specialist care through European Reference Networks

In 2017 the European Commission established 24 ERNs for rare diseases to enable patients with rare and complex conditions to benefit from the best treatment and advice for their condition that is available in the EU.[46] Each ERN focuses on a specific group of rare or low-prevalence complex diseases. At the moment, specialised healthcare teams in more than 300 hospitals in 26 European countries are involved.[47] These are predominantly EU states but include other countries in the European Economic Area (EEA), such as Norway, and the UK remains a member despite Brexit.

One of these is the ERN on Hereditary Metabolic Disorders (MetabERN),[48] which is led by Professor Scarpa. This currently includes 78 hospitals in 23 countries, he says, and another 24 hospitals are due to join by the end of 2021, at which point nearly all countries in the EU will be represented.

There are also ERNs on rare neuromuscular disorders (ERN-NMD) and rare neurological diseases (ERN-RND).

[44] Simpson A, Bloom L, Fulop N J et al, "How are patients with rare diseases and their carers in the UK impacted by the way care is coordinated? An exploratory qualitative interview study", Orphanet J Rare Dis 16, 76 (2021), https://doi.org/10.1186/s13023-020-01664-6

[45] Sestini S, Paneghetti L, Lampe C et al, "Social and medical needs of rare metabolic patients: results from a MetabERN survey", *Orphanet J Rare Dis,* 16, 336 (2021), https://doi.org/10.1186/s13023-021-01948-5

[46] https://ec.europa.eu/health/ern_en Accessed October 5th 2021

[47] Ibid

[48] https://metab.ern-net.eu/ Accessed October 5th 2021.

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The European Reference Networks (ERNs) develop guidelines and consensus papers, facilitate training and knowledge exchange, link with the major patient organisations, and undertake research to improve understanding of the disease and management of patients.

The ERNs enable specialists to share knowledge and expertise and use a dedicated IT platform—the Clinical Patient Management System—and telemedicine tools to convene multidisciplinary virtual panels to review patients and manage their care.[49,50]

There are around 3,000 health professionals working in MetabERN following more than 60,000 patients, says Professor Scarpa.

The ERNs also develop guidelines and consensus papers, facilitate training and knowledge exchange, link with the major patient organisations, and undertake research and other projects to improve understanding of the disease and management of patients.[51] They develop diagnostic flowcharts and disease scales to assess different aspects of rare neurological diseases to try to improve the speed and accuracy of diagnosis,[52] and to discuss an unclear diagnosis to try to provide an answer for patients and families and improve the diagnostic criteria for future patients.[53]

ERNs are helping to standardise treatment and provide equitable access to care for rare neurological disorders across Europe, as guidelines and care have varied between countries, interviewees say.

Ms Dan says the ERNs are "a big achievement" for the EU Cross Border Healthcare Directive, and are particularly helpful for patients and families in countries that have fewer experts, "but it could work better". (See "Difficulties accessing therapies and cross-border healthcare" below.)

The network is focused on different sites and their experts to support exchanges, and to support sites and centres that lack expertise in certain diseases.

For example, there may be a centre that has very solid expertise in general neurological diseases, but not in LSDs, Mr Mentzel says. "They could use this network to discuss the case and treatment as the diagnosis is one thing, but you also need, of course, the support on how to follow up. Here, I think this network can be even more helpful. What are the therapeutic options and supportive therapies for these conditions?"

Some patient groups are concerned about the impact of Brexit on the involvement of UK-based clinicians and the care of their UK-based patients via ERNs. "We're not sure what influence or input UK clinicians will have going forward," says Ms Mathieson, "and what the repercussions will be for the patient networks that have been formed."

[49] Reinhard C, Bachoud-Lévi AC, Bäumer T, Bertini E, Brunelle A, Buizer AI, Federico A, Gasser T, Groeschel S, Hermanns S, Klockgether T, Krägeloh-Mann I, Landwehrmeyer GB, Leber I, Macaya A, Mariotti C, Meissner WG, Molnar MJ, Nonnekes J, Ortigoza Escobar JD, Pérez Dueñas B, Renna Linton L, Schöls L, Schuele R, Tijssen MAJ, Vandenberghe R, Volkmer A, Wolf NI, Graessner H, "The European Reference Network for Rare Neurological Diseases", *Front Neurol, 2021 Jan 14;11:616569, doi: 10.3389/fneur.2020.616569, PMID: 33519696; PMCID: PMC7840612*

[50] https://ec.europa.eu/health/ern/work_en Accessed October 5th 2021

[51] Ibid

[52] Reinhard C, Bachoud-Lévi AC, Bäumer T, Bertini E, Brunelle A, Buizer AI, Federico A, Gasser T, Groeschel S, Hermanns S, Klockgether T, Krägeloh-Mann I, Landwehrmeyer GB, Leber I, Macaya A, Mariotti C, Meissner WG, Molnar MJ, Nonnekes J, Ortigoza Escobar JD, Pérez Dueñas B, Renna Linton L, Schöls L, Schuele R, Tijssen MAJ, Vandenberghe R, Volkmer A, Wolf NI, Graessner H, "The European Reference Network for Rare Neurological Diseases", *Front Neurol, 2021 Jan 14;11:616569, doi: 10.3389/fneur.2020.616569, PMID: 33519696; PMCID: PMC7840612*

[53] *Ibid*

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Further training for doctors and other health professionals

Training in recognising and managing rare neurological diseases is lacking at all levels—specialist doctor, GPs, nurse and allied health professional. For instance, a study in Spain found that less than a third of physicians had received training in rare diseases during their undergraduate or postgraduate years, and hospital professionals received more training in the postgraduate period.[54] A study in Poland found that nearly 95% of physicians thought their knowledge on rare conditions was insufficient/very poor, and less than 5% felt they were equipped to care for patients with such conditions.[55]

"In Europe, there is no special and specific teaching of rare diseases anywhere," says Professor Scarpa.

As a result, the ERN-RND has set up a training and education programme for doctors on rare neurological diseases to expand expertise among neurologists,[56,57] and MetabERN is working on a curriculum on rare diseases for metabolic specialists.

It is not just specialists that need training on rare conditions, but also the wider healthcare workforce, he says. "The problem for rare disease patients is that they need more help from GPs, so we need to instruct and educate GPs about rare diseases. This is a major challenge, because the general education of rare diseases is pretty low for most doctors who are not specialists."

Interviewees believe that rare diseases as a course should be part of the curriculum of all new doctors, which is currently a gap. "We are working with the European Commission on this, but it will take time, at least the next five years," says Professor Scarpa.

There are around 60,000 conditions, and in 35 years a doctor will see about 2,500, so it is not about being a specialist in everything, says Professor Scarpa. He would like to see primary care physicians sending more patients to specialist centre with queries: is this a rare disease or not? "I would be happier to send a patient back and say, 'No this is not a rare disease, continue with your work', rather than missing a patient."

Registries support clinical research

A patient registry can be a powerful tool to observe how a disease progresses, understand variations and impact of treatment, outcomes and quality of life, and in the appropriateness and disparities in the delivery of care.[58] They are also important for research.

The likelihood that a treatment will be developed for a disease increases when a disease has well-implemented disease registries and active patient organisations that can assist recruitment of patients for research studies.[59] Even in the absence of research and development of new therapies, the consistent collection of longitudinal patient data helps in the development of standards of care and markedly improves patient outcomes.[60]

[54] Ramalle-Gómara E, Domínguez-Garrido E, Gómez-Eguílaz M et al, "Education and information needs for physicians about rare diseases in Spain", *Orphanet J Rare Dis*, 15, 18 (2020), https://doi.org/10.1186/s13023-019-1285-0

[55] Walkowiak, D., Domaradzki, J. Are rare diseases overlooked by medical education? Awareness of rare diseases among physicians in Poland: an explanatory study. *Orphanet J Rare Dis* **16,** 400 (2021). https://doi.org/10.1186/s13023-021-02023-9

[56] Reinhard C, Bachoud-Lévi AC, Bäumer T, Bertini E, Brunelle A, Buizer AI, Federico A, Gasser T, Groeschel S, Hermanns S, Klockgether T, Krägeloh-Mann I, Landwehrmeyer GB, Leber I, Macaya A, Mariotti C, Meissner WG, Molnar MJ, Nonnekes J, Ortigoza Escobar JD, Pérez Dueñas B, Renna Linton L, Schöls L, Schuele R, Tijssen MAJ, Vandenberghe R, Volkmer A, Wolf NI, Graessner H, "The European Reference Network for Rare Neurological Diseases", *Front Neurol, 2021 Jan 14;11:616569, doi: 10.3389/fneur.2020.616569, PMID: 33519696; PMCID: PMC7840612*

[57] https://www.ern-rnd.eu/education-training/ Accessed October 6th 2021

[58] Gliklich R E, Dreyer N A, Leavy M B, editors, "Registries for Evaluating Patient Outcomes: A User's Guide" [Internet], 3rd edition, Rockville (MD), Agency for Healthcare Research and Quality (US), 2014 April 1st, Patient Registries, https://www.ncbi.nlm.nih.gov/books/NBK208643/

[59] Eurordis Factsheet, Rare Disease Patient Registries, 2013

[60] ibid

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"Wider national and international registries that combine wider disease groups, for example, all inherited metabolic diseases or lysosomal storage diseases, are needed in addition. But it's so difficult and so expensive to put together."

Toni Mathieson, chief executive of Niemann-Pick UK.

A multitude of registries and other data capture systems currently exist within Europe and collect data at different levels—within hospitals, across regions and countries, for specific diseases, and across research networks. As a result, there is a wide range of data that could aid patient care and research purposes, which are not readily accessible. Full interoperability between these registries would open access to a rich and unique source of health data,[61] but this requires systems to be compatible and ideally underpinned by an electronic health record system.[62]

The EC set up a European Platform on Rare Disease Registration to develop specific standards for the interoperability of rare disease registries,[63] because around 30 million EU citizens are affected by more than 6,000 different rare diseases and the information about these patients is spread between hundreds of registries across Europe.[64] The aim of this initiative is to standardise collection and exchange of registry data and make registries searchable at EU level, which will increase the value of these registries and the benefits to patients included on them.[65]

The ERNs are creating registries of patients and providing a unique overview of existing genotype-based cohorts to aid patient recruitment into clinical trials.[66]

The data collected in the registries also provide information on the geographical location of patients, whether they experience the same symptoms and if specific mutations occur in certain countries or regions, say interviewees.

"One downside of the ERN registries might be that they only include patients associated with clinics at the specialised centres that are part of the ERNs," points out Mr Mentzel.

Historically, registries have been focused around the treatment the patient has or is receiving, so have been set up by companies or research teams using a specific product, Ms Mathieson says, but more recently there has been a move towards creating registries of patients with specific diseases. These are often limited in scope, just for patients treated by a specific research team or at academic institutions, or have links with a specific patient organisation. Wider national and international registries that combine wider disease groups, for example, all inherited metabolic diseases or LSDs, are needed in addition, she says. "But it's so difficult and so expensive to put together."

[61] Nicholson N, Perego A, "Interoperability of population-based patient registries", J Biomed Inform X, 2020 Sep;6:100074, doi: 10.1016/j.yjbinx.2020.100074, Epub 2020 Jun 13, PMID: 32838295; PMCID: PMC7293468

[62] Ehrenstein V, Kharrazi H, Lehmann H, et al, "Obtaining Data From Electronic Health Records", In: Gliklich RE, Leavy MB, Dreyer NA, editors, "Tools and Technologies for Registry Interoperability, Registries for Evaluating Patient Outcomes: A User's Guide, 3rd Edition", Addendum 2 [Internet], Rockville (MD): Agency for Healthcare Research and Quality (US); 2019 Oct, Chapter 4, Available from: https://www.ncbi.nlm.nih.gov/books/NBK551878/

[63] "Rare disease registries for the European Reference Networks", July 6th 2019, https://echalliance.com/rare-disease-registries-for-the-european-reference-networks/

[64] https://eu-rd-platform.jrc.ec.europa.eu/_en Accessed November 24th 2021

[65] Ibid

[66] Reinhard C, Bachoud-Lévi AC, Bäumer T, Bertini E, Brunelle A, Buizer AI, Federico A, Gasser T, Groeschel S, Hermanns S, Klockgether T, Krägeloh-Mann I, Landwehrmeyer GB, Leber I, Macaya A, Mariotti C, Meissner WG, Molnar MJ, Nonnekes J, Ortigoza Escobar JD, Pérez Dueñas B, Renna Linton L, Schöls L, Schuele R, Tijssen MAJ, Vandenberghe R, Volkmer A, Wolf NI, Graessner H, "The European Reference Network for Rare Neurological Diseases", *Front Neurol, 2021 Jan 14;11:616569, doi: 10.3389/fneur.2020.616569, PMID: 33519696; PMCID: PMC7840612*

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She explains: "It helps industry, helps researchers, it helps everyone to understand where the patients are, what point they are in their disease, and what their unmet needs are."

Comprehensive registries would help support recruitment into clinical trials. Currently patient support groups try to fill the gap, says Mr Mentzel. "If a clinician wants to do a study, it's me who is calling up patients and signposting them to the study." Ideally registry data should be linked with corresponding biobanks data to facilitate this.[67]

Difficulties accessing therapies and cross-border healthcare

In an age of genomic research and better understanding around rare disease variants, diagnoses of rare paediatric neurological conditions are rising alongside innovative therapeutic approaches. More than 800 gene and cell therapy programmes and eight therapies have received approval from the European Medicines Agency and the US Food and Drug Administration,[68] meaning healthcare systems need to better deal with financing these advanced therapies. Around 20 gene-based therapies are expected to receive approval by 2025.[69]

Although expensive, the majority of these gene therapies are considered one-off treatments, meaning that the costs of further treatment and care for these patients are expected to be reduced,[70,71,72,73,74] although the funder of the gene therapy may not be the beneficiary, especially in countries with competitive health insurance systems.[75] As many of these treatments are so new, at this stage it is unclear whether some patients might need some further treatment in later life, Ms Mathieson says. "We're not sure about that yet. Perhaps in five or ten years, they might need a top-up of some description. Obviously, it wouldn't be that same gene therapy, but it might be that they needed a therapy that works in combination with that first treatment to help the disease to remain stable."

Some rare neurological disorders do not have an effective treatment, and where an effective treatment exists, families may struggle to access it because the healthcare system in their country does not fund or provide it.

This is particularly the case with the newest and most innovative treatments, says Ms Mathieson, because they are seen as so expensive.

Most countries in Europe have modified their usual appraisal and reimbursement mechanisms

[67] *EURORDIS Factsheet, Rare Disease Patient Registries, 2013*

[68] *Privolizzi R, Sum Chu W, Tijani M, Ng J, "Viral gene therapy for paediatric neurological diseases: progress to clinical reality", Developmental Medicine & Child Neurology, April 2021, DOI 10.1111/dmcn.1488509 https://doi.org/10.1111/dmcn.14885*

[69] *Ibid*

[70] *Garrison L P Jr, Jiao B, Dabbous O, "Gene therapy may not be as expensive as people think: challenges in assessing the value of single and short-term therapies", J Manag Care Spec Pharm, 2021 May;27(5):674-681. doi: 10.18553/jmcp.2021.27.5.674, PMID: 33908277*

[71] *Machin N, Ragni M V, Smith K J, "Gene therapy in hemophilia A: a cost-effectiveness analysis", Blood Adv, 2018;2(14):1792-1798, doi:10.1182/bloodadvances.2018021345*

[72] https://www.mckinsey.com/industries/life-sciences/our-insights/gene-therapy-coming-of-age-opportunities-and-challenges-to-getting-ahead Accessed November 3rd 2021

[73] Jesper Jørgensen, Eve Hanna and Panos Kefalas, "Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries", *Journal of Market Access & Health Policy, 2020, 8:1, 1715536, DOI: 10.1080/20016689.2020.1715536*

[74] *Towse A, Fenwick E, "Uncertainty and Cures: Discontinuation, Irreversibility, and Outcomes-Based Payments: What Is Different About a One-Off Treatment?" Value Health, 2019 Jun;22(6):677-683. doi: 10.1016/j.jval.2019.03.013. PMID: 31198185.*

[75] *Danzon P, Towse A, "The economics of gene therapy and of pharmacogenetics", Value Health, 2002 Jan-Feb;5(1):5-13, doi: 10.1046/j.1524-4733.2002.51081.x, PMID: 11873384.*

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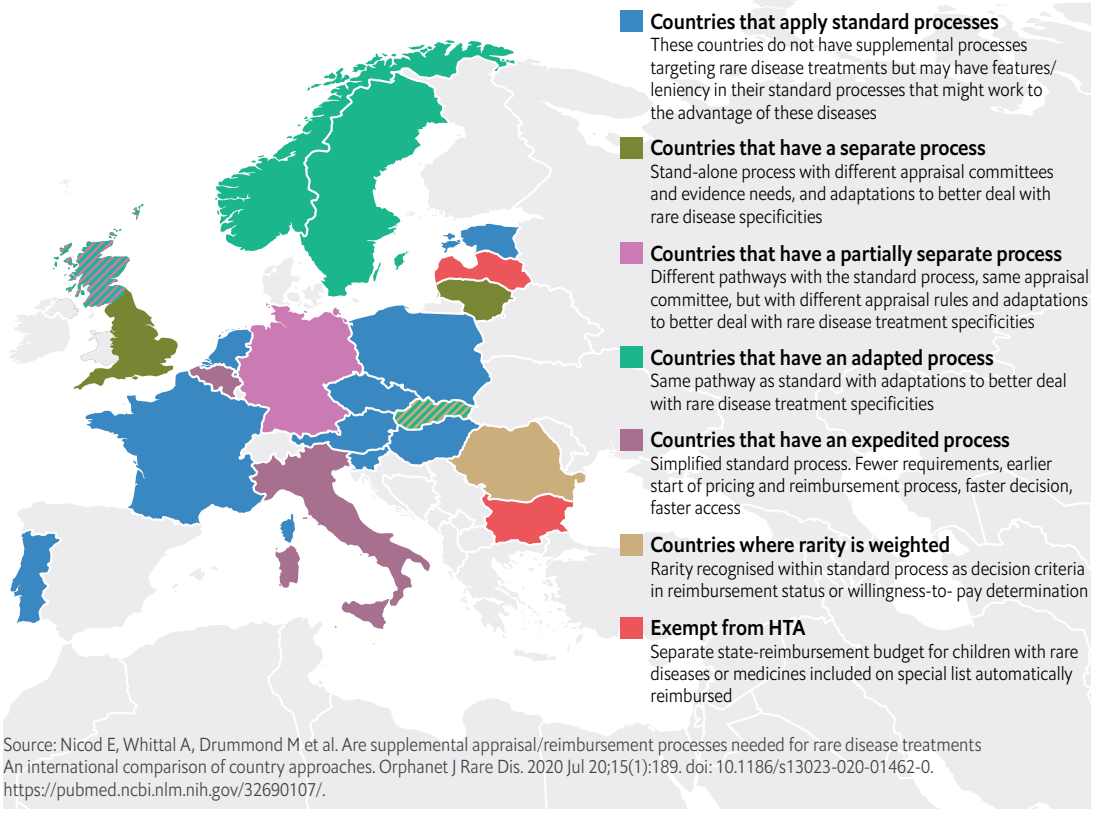
or adopted specific ones for rare condition treatments to take account for the fact that smaller patient populations make it harder for the company that developed a treatment to recoup their research costs, but these vary markedly between countries (Figure 7). Researchers, with funding from the EC's Horizon 2020 programme, say that as more treatments for rare diseases become available, it is important that national appraisal approaches are transparent to ensure that decisions are fair and accountable within countries, but also to provide the potential to develop a common appraisal framework across Europe.[76] Ultimately, countries are still adjusting processes.

"The reimbursement or payment back to the company is spread not over millions of patients but a few hundred," explains Professor Scarpa, "so some countries with a low income will not fund that therapy."

Figure 7: Examples of health technology appraisal/reimbursement processes for rare disease treatments in Europe



Source: Nicod E, Whittal A, Drummond M et al. Are supplemental appraisal/reimbursement processes needed for rare disease treatments An international comparison of country approaches. Orphanet J Rare Dis. 2020 Jul 20;15(1):189. doi: 10.1186/s13023-020-01462-0. https://pubmed.ncbi.nlm.nih.gov/32690107/.

[76] Nicod E, Whittal A, Drummond M *et al, "Are supplemental appraisal/reimbursement processes needed for rare disease treatments? An international comparison of country approaches", Orphanet J Rare Dis*, 15, 189 (2020), https://doi.org/10.1186/s13023-020-01462-0

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"High-cost therapies have to be matched against the real-life cost burden of the condition, which can be enormous."

Tim Cox, professor of medicine emeritus and director of research at the University of Cambridge; honorary consultant physician in metabolic medicine at Addenbrooke's Hospital, Cambridge, UK

"In some cases, children need to have these treatments very quickly in order to stop very debilitating symptoms, and this may not happen because the decision-making process around reimbursement is too slow, which is just so disappointing," Ms Mathieson says.

Patient groups believe that decision-makers should think longer term and consider a wider range of factors. "They should look further ahead into the future and not just look at the budget for the year and that this treatment costs £350,000, if it's going to change the lives of these children and then allow them to go to school to learn, to achieve their contribution to society and allow their parents to continue contributing to society," adds Ms Mathieson.

Professor Cox agrees. "High-cost therapies have to be matched against the real-life cost burden of the condition, which can be enormous," he says. These costs include the alternative healthcare costs of caring for the patient with standard treatment and supportive care, the loss of income for the parents and the child and any benefits that would be paid, as well as the deep and pervasive human costs. These include the strain on family relationships and day-to-day anxieties, as well as the emotional pressure of seeing a loved child or relative suffer from pain and, as so often happens, the relentless loss of skills, mobility and sensation. "Irrespective of the costs of a given therapy, I contend that the primary job of the doctor under these circumstances is to argue for the patient in front of them with the regulators for the financing of effective treatment," he says.

Certain treatments for rare neurological conditions are not available in some countries, particularly smaller countries, meaning that patients will need to travel to a country that provides the planned healthcare they require. Two pieces of EU legislation facilitate planned treatment to take place within other countries within the EEA: Social Security Regulations (EC) 883/2004 and 987/2009 (the regulation) and the Directive 2011/24/EU on patients' rights in cross-border healthcare (the directive).[77] There are differences between the two legal instruments in the conditions and the range of healthcare services covered, and also how the patient is reimbursed (Table 3).

[77] https://ec.europa.eu/health/sites/default/files/cross_border_care/docs/2019_ncptoolbox_manualpatients_en.pdf Accessed October 5th 2021

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Table 3: Comparison of patients' rights to cross-border healthcare under the Directive and the Regulation

	DIRECTIVE	REGULATION
Sector	Public + Private	Public only
Eligible treatments	Treatments available under patients' own country's health-insurance	Treatments available under the other country's national health-insurance
Prior authorisation	Required under certain circumstances	Always required for planned care Not required for emergency situations
Costs covered	Reimbursement up to the amount had the treatment been carried out in patients' home country	Complete funding (barring co-payment charges)
Reimbursement of co-payment charges	Up to the limit of the cost in the home country	Yes (under certain conditions)
Method of payment	Patients pay up-front and are reimbursed at a later time (reimbursement-system)	Between countries, no up-front payment from patients required (funding-system)
Eligible countries	All EU & EEA countries	All EU & EEA countries + Switzerland
Number of citizens claiming reimbursement for medical care received abroad	Under the Directive: 200 000 claims a year (fewer than 0.05% of EU citizens)	Under Regulation: Around 2 million claims a year for unplanned treatments abroad

Source: European Court of Auditors. EU actions for cross-border healthcare: significant ambitions but improved management required, 2019.

Under the regulation, patients are entitled to treatment in another EU/EEA country or Switzerland as though they were insured under the social security system of that country. Patients always need prior authorisation from the national health service/statutory health insurance provider in the country under whose social security system they are insured. If the authorisation is granted, the costs of the treatment are covered according to the conditions and reimbursement rates of the public health system in the country where they will be treated. Patients may have to cover certain fees applied to patients in the country to which they travel, and private healthcare is not eligible for reimbursement. These costs are normally paid directly by the insurer or the health system to the institution in the country of treatment, so the patient does not have to pay upfront.

Under the directive, patients are entitled to treatment in either the public or private healthcare system in an EU/EEA country as though the treatment was provided in their home country. Patients have to pay all medical costs upfront and then claim reimbursement from their national health service/health insurance provider, which will be reimbursed according to the domestic tariffs applied for the same treatment in their home country. Generally, prior authorisation from the home country's national health service/health insurance provider is not required, but for some treatments member states have discretion to install a system of prior

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An effective EU cross-border healthcare framework is critical to enable patient access to gene therapies and other advanced therapy medicinal products (ATMPs) for severe and rare genetic diseases.

authorisation. Following Brexit, people from the UK can only apply for reimbursement for treatment that started or was approved before 11pm on 31 December 2020.[78]

The requirement for upfront payment by the patient under the directive means that the pathway under the regulation is the only viable route for patients seeking access to expensive treatments, such as gene and cell therapies.[79]

The number of people using the directive to claim reimbursement for medical care received abroad is miniscule compared with those making use of the regulation, approximately 200,000 (less than 0.05% of EU citizens) and 2 million claims a year, respectively.[80] A 2015 Eurobarometer survey reported that less than 20% of citizens understood their rights to cross-border healthcare.[81]

An effective EU cross-border healthcare framework is critical to enable patient access to gene therapies and other advanced therapy medicinal products (ATMPs) for severe and rare genetic diseases. Members of the European Parliament are concerned that the current framework does not work for patients in practice. As the directive places the burden of upfront payments on patients, the regulation is currently the only viable route for cross-border ATMP treatment. Gaining approval through the regulation is not easy, as it can be a complex process, with varying approval timelines across the EU, which means patient access to potentially curative therapies can be denied or delayed.[82]

The EC is reviewing the Cross-border Healthcare Directive and that evaluation is expected to be completed in 2022. "The Commission's evaluation of the directive will assess to what extent the directive has contributed to removing obstacles to access to healthcare in another Member State and to be reimbursed for the medical costs, including for rare disease patients, and what factors have hindered this," says Stella Kyriakides, EU health commissioner.[83]

Some countries, especially richer countries such as Germany and France, have strong expanded access or compassionate use programmes, which enable patients to get early access to investigational therapies outside of clinical trial settings, Ms Mathieson says.

But sometimes these therapies are only available within clinical trials, and even then patients in some of the richest countries in Europe struggle to access them. "We've seen issues with patients accessing therapies in Norway and other Scandinavian countries. There are such small numbers of patients in those countries, so they don't tend to have a trial site and some of the countries, such as Germany will close their trial

[78] https://www.nhs.uk/using-the-nhs/healthcare-abroad/going-abroad-for-treatment/going-abroad-for-medical-treatment/Accessed December 11th 2021

[79] http://www.pmlive.com/pharma_intelligence/EU_cross-border_healthcare_1368024?SQ_DESIGN_NAME=2& Accessed October 5th 2021

[80] European Court of Auditors, "EU actions for cross-border healthcare: significant ambitions but improved management required", 2019

[81] Ibid

[82] European Parliament, Parliamentary question, June 2nd 2021, https://www.europarl.europa.eu/doceo/document/E-9-2021-002940_EN.html Accessed November 1st 2021

[83] Answer to parliamentary question, August 4th 2021, https://www.europarl.europa.eu/doceo/document/E-9-2021-002940-ASW_EN.html Accessed November 1st 2021

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sites to outside patients, because they have such high numbers wishing to access them from their own country," she says.

Transitioning from paediatric to adult services

As children grow into adults, parents can usually take pleasure in watching them leave home, embarking on careers and making their own life decisions. But for parents of children with rare neurological disorders, this is an extremely worrying time.

When they leave school and reach adulthood, the help and support available "completely changes,", says Ms Mathieson. "There aren't any job opportunities, if you want to send them to a day centre, it's often populated by older people."

Then there are the wider social issues.

A lot of young adults who have been treated for many years and are doing well but still have cognitive issues are desperate to participate in social activities and to be seen as normal by their peers, she says. "They don't have any opportunities to do that. It is a big problem for us—–what do they do around meeting young people and dating?"

The MetabERN study of patients with rare inherited metabolic diseases in Europe found that access to services to support the transition from childhood to adulthood was limited and only available to 16-29% of patients.[84] In most cases, respondents did not know about or had not been told about meeting places for young people that were easily accessible for those with disabilities, vocational training programmes, autonomy-development pathways or independent life experiences.

Patients also transition from paediatric to adult medical teams. This means that when they have to go into hospital, parents are prevented from attending and are unable to stay in hospital with their children to provide additional care, as they would have done when they were treated by paediatric services.

"The hospitals don't see the cognitive issues of neurological conditions and they don't give them one-to-one care," Ms Mathieson says. "That's hugely difficult and has caused issues that have been life threatening in some cases."

Vital role of patient advocacy organisations

As well as supporting patients with rare neurological diseases, patient groups and representatives have a huge role in promoting research into the understanding of the disease process and potential treatment of these conditions and influencing the policy frameworks that determine the care patients will receive.

"Most patient organisations provide a really high level of information, and it is really important that patients and families can access accurate information and that they have access to other people affected with the condition that they can identify with. I think that really helps to alleviate anxiety and for people to feel part of a community," says Ms Mathieson.

However, the predominance of patient groups and what they can achieve varies between countries.

In the UK, for example, many patient organisations have paid staff, advocacy teams that can provide advice on services, schools, home adaptions, social care and benefits and help families negotiate the systems, and some,

[84] Sestini S, Paneghetti L, Lampe C et al, "Social and medical needs of rare metabolic patients: results from a MetabERN survey", *Orphanet J Rare Dis, 16, 336 (2021), https://doi.org/10.1186/s13023-021-01948-5*

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"If you're a volunteer parent who is holding down a full-time job and looking after your sick child, then you don't have that time. Unfortunately, this is what we are seeing in many of the [patient] groups in Europe."

Toni Mathieson, chief executive of Niemann-Pick UK.

such as the UK LSD Patient Collaborative, even provide patients with access to a dedicated clinical nurse specialist with expertise on their condition, says Ms Mathieson, who is chair of the collaborative. "They're all very well set up and able to lobby the government for improvements. While patient organisations do exist in other countries, they're not often as well resourced, or don't have the capacity of paid employees who are able to carry out all the tasks that are needed to fill care and support gaps," says Ms Mathieson.

"If you're a volunteer parent who is holding down a full-time job and looking after your sick child, then you don't have that time. Unfortunately, this is what we are seeing in many of the groups in Europe."

Patient groups also help families connect with research groups investigating their child's condition. There are very few patients with SSADH, which affects Ms Ríos Aroca's daughter, but she says that through De Neu they are in touch with a research team in the US who has been investigating the condition for 20 years. "They are very active. We are very lucky because they are investigating. Although we still don't have a treatment, at least we have support from them," she says.

The focus on rare diseases has increased markedly in the past 20 years in Europe, as a result of lobbying from patients who believed they were receiving second-class care, states Professor Scarpa. "Their efforts have been fundamental to the establishment of the ERNs and the cross-border healthcare legislation," he says.

Better understanding of rare neurological disorders—in terms of their underlying disease processes and how to treat them—has been "instrumental" to increasing our understanding of more common conditions. "Quite a lot of our knowledge of Parkinson's disease and multiple sclerosis has come from LSDs," says Professor Scarpa. This is because the lysosome is the filter for molecules, such as the amyloid and P protein that are implicated in many common neurodegenerative diseases.[85] "So it is important to study these disorders to even understand more common diseases," he says.

[85] Hwang J, Estick C M, Ikonne U S, Butler D, Pait M C, Elliott L H, Ruiz S, Smith K, Rentschler K M, Mundell C, Almeida M F, Stumbling Bear N, Locklear J P, Abumohsen Y, Ivey C M, Farizatto K L G, Bahr B A, "The Role of Lysosomes in a Broad Disease-Modifying Approach Evaluated across Transgenic Mouse Models of Alzheimer's Disease and Parkinson's Disease and Models of Mild Cognitive Impairment", *Int J Mol Sci*, 2019 Sep 9;20(18):4432, doi: 10.3390/ijms20184432, PMID: 31505809; PMCID: PMC6770842

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Conclusion and policy takeaways

Life for children with rare neurological disorders and their families is difficult on personal, medical, social and financial fronts. While these conditions individually are rare, there are multiple types. And although symptoms differ between conditions, there is a common theme: these disorders affect multiple organs and systems, they are degenerative and place a huge burden on families and caregivers, so patients need specialist and multidisciplinary care.

Diagnosis is a key challenge. For many neurotransmitter disorders and LSDs, early diagnosis is essential for the best outcomes; and treatments need to be commenced as soon as possible to impact the biological pathways in a life-changing and irreversible way. For many conditions there is a limited window of time to diagnose and treat children before the damage becomes irreversible or cognitive and developmental milestones are missed.

With European policymakers and healthcare providers in mind, policy takeaways for improving care are therefore focused around ensuring prompt diagnosis and effective care.

Standardised neonatal screening policies embedded within national health systems: screening at birth or during pregnancy helps ensure an early diagnosis that removes the diagnostic odyssey and is essential for the treatment of some conditions. Use of genetic screening is variable across Europe and needs to be increased and standardised, because embedding the screening for certain conditions within all national health systems is the only way to guarantee every child has the right to health. Currently there is a marked variation in the provision of newborn screening, with some countries testing for only one or two conditions. However, Italy is considered a leader, as it has mandatory screening at birth for more than 40 conditions and reviews its screening panel every two years. EURORDIS is campaigning for Italian newborn screening to be endorsed as best practice and replicated across Europe.

More genetic counsellors and greater access to them: there is a shortage of genetic counsellors and analysts of genetic data across Europe, which means only the immediate family of an affected patient may be able to access these services. When a child is diagnosed with a rare inherited neurological condition, it is understandably unsettling for the wider family who will be concerned that any existing or future

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children may be affected. In addition, a lack of access to these services can deter some from starting or increasing their family.

Further training for all doctors in rare conditions: in Europe, there is no specific medical curriculum for rare diseases, but this needs to be made part of the curriculum of new doctors. This does not mean that all doctors should be trained in all rare diseases, but know instead when to be suspicious for rare diseases and where they can make rapid referrals for further investigation. Many neurodegenerative diseases have a common pattern of disability that requires the same diagnostic skill set; this can be brought to bear quite quickly once the referral is made to the appropriate specialist. Better training will also improve care for patients. While patient care should continue to be managed by specialist centres, most patients live far from these and need to receive day-to-day care from local services.

Improved access to, and collaboration between specialist centres: the EC launched 24 ERNs including one for metabolic disorders, which includes 78 hospitals in 23 countries and another 24 by the end of 2021. The ERNs have improved care for patients: they convene multidisciplinary virtual panels to review patients and manage their care, hone diagnostic criteria and develop diagnostic flow charts to improve the speed of diagnosis, and develop guidelines to improve care. However, there is more work to do. The ERNs need to be expanded, as collaboration is only between participating hospitals, meaning doctors working elsewhere cannot seek support and advice to benefit their patients.

Interoperable and comprehensive registries needed: registries are essential tools for research, care and connecting families. European registries that include all patients with rare neurological disorders are needed. Comprehensive registries would provide information on the geographical location of patients, patterns of symptoms and whether specific mutations occur in certain countries or regions. These data would benefit research, particularly recruitment into clinical trials. Existing registries have limitations, generally covering specific hospitals, regions, countries or research networks and do not include comprehensive data. Full interoperability between these registries, ideally underpinned by electronic patient record systems, would open up access to a rich and unique source of health data to aid patient care and research. The ERNs are beginning to build registries, but they only include patients associated with the clinics that are part of the ERN. The EC set up a European Platform on Rare Disease Registration to develop specific standards for the interoperability of rare disease registries across Europe. It aims to make registries' data searchable at EU level by standardising data collection and data exchange, which will increase the value of each registry and its registration.

A more patient-friendly cross-border healthcare framework: in some countries, patients are not able to access the latest innovative treatments because the healthcare system does not have the specialist centres and expertise to provide to them. Patients must then travel to other countries to receive treatment. Although this is possible under EU cross-border healthcare legislation—the directive and the regulation—the system could be improved to better meet the needs of patients with rare diseases requiring advanced therapies. Under the directive, patients have to pay for their care upfront and reclaim it from their national health system, so due to the high cost of such therapies, the regulation is currently the only viable route for cross-border treatment. However, it is a complex instrument; an opaque approval process and varying approval timelines across the EU can delay or block access to potentially curative

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treatment. The EC is reviewing the directive, which is expected to be completed in 2022. When innovative treatments are only available through clinical trials, patients may not be able to access them if they do not live in a country with a trial site, as these sites often prioritise patients in their own country when demand is high.

Funding models need to take more account of the unique nature of rare diseases and their management: most countries in Europe have modified their usual appraisal and reimbursement mechanisms or developed specific ones for therapies for rare diseases. However, in many cases treatments remain unavailable because the cost per patient necessary to recoup their development is far higher than it is for more common conditions. Funding models that better explore and take into account the rareness of conditions and also their wider cost benefits, such as reduced healthcare and support costs, potential productivity to society of both parents and patients, and improved quality of life, are needed. Many genetic therapies may only need to be given once and can prevent irreversible complications for a child, which would have placed a heavy burden on the family and society for the rest of their life; one-off costs may be high, so further investigation into their cost-benefit balance is needed.

Improve the quality of life and wellbeing of the child and family: as these conditions place a heavy burden on the entire family, more support is needed. Financial strain on families is often very high, as at least one parent usually has to give up work to care for the child. In many countries, families struggle to access supportive care, palliative care, appropriate schools and opportunities for their child to socialise. Care pathways need to acknowledge these situations and encourage greater provision.

Patient groups need more support, as they act as linchpins for families and carers: patient groups offer a hub of support for patients and their families. Not only are they a key a source of information and advice, they connect families so that they can share experiences and interact socially with each other. They fill gaps by advising families on services and helping them negotiate access, and alerting them to medical advances and clinical trial opportunities. In some cases, they provide services such as access to clinical nurse specialists experienced in a particular disease. In many cases, these organisations are run by volunteers and need more support.

Using the evidence from this report, European policy-makers and healthcare providers can work together to bring forth solutions for children (and their families) living with rare paediatric neurological conditions.

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Appendix 1

Table 4: Orphanet classification of rare neurological disease groups.
Many of these conditions also affect children. The Orphanet also classifies disease groups under "rare inborn errors of metabolism" and "rare genetic diseases", so there is crossover.

Rare neurologic disease ORPHA:98006
Alternating hemiplegia ORPHA:209978
Arachnoiditis ORPHA:137817
Athabaskan brainstem dysgenesis syndrome ORPHA:69739
Balint syndrome ORPHA:363746
Brain calcification, Rajab type ORPHA:178506
Central nervous system malformation ORPHA:98044
Complex regional pain syndrome ORPHA:83452
Flynn-Aird syndrome ORPHA:2047
Gerstmann syndrome ORPHA:221117
Idiopathic intracranial hypertension ORPHA:238624
Idiopathic recurrent stupor ORPHA:276174
Infectious disease of the nervous system ORPHA:98010
Inherited congenital spastic tetraplegia ORPHA:210141
Inherited nervous system cancer-predisposing syndrome ORPHA:252190
KLHL7-related disorder ORPHA:603699
Leukodystrophy ORPHA:68356
Locked-in syndrome ORPHA:2406
Medullar disease ORPHA:102000
Moderate and severe traumatic brain injury ORPHA:90056

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Table 4 (continued): Orphanet classification of rare neurological disease groups.
Many of these conditions also affect children. The Orphanet also classifies disease groups under "rare inborn errors of metabolism" and "rare genetic diseases", so there is crossover.

Neonatal brainstem dysfunction ORPHA:137929

Neurometabolic disease ORPHA:68385

Paroxysmal extreme pain disorder ORPHA:46348

Perineural cyst ORPHA:65250

Persistent idiopathic facial pain ORPHA:398147

Primary orthostatic disorder ORPHA:521236

Rare ataxia ORPHA:102002

Rare autonomic nervous system disorder ORPHA:423662

Rare central nervous system and retinal vascular disease ORPHA:71281

Rare disease with malignant hyperthermia ORPHA:466658

Rare epilepsy ORPHA:101998

Rare headache ORPHA:98022

Rare intellectual disability ORPHA:87277

Rare movement disorder ORPHA:102003

Rare nervous system tumor ORPHA:98062

Rare neurodegenerative disease ORPHA:182070

Rare neuroinflammatory or neuroimmunological disease ORPHA:182064

Rare neurologic disease with psychiatric involvement ORPHA:98033

Rare peripheral neuropathy ORPHA:98496

Rare sleep disorder ORPHA:68354

Secondary erythromelalgia ORPHA:529864

Specific learning disability ORPHA:211047

Spinal cord injury ORPHA:90058

Spontaneous periodic hypothermia ORPHA:29822

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Table 4 (continued): Orphanet classification of rare neurological disease groups.
Many of these conditions also affect children. The Orphanet also classifies disease groups under "rare inborn errors of metabolism" and "rare genetic diseases", so there is crossover.

Symmetrical thalamic calcifications ORPHA:1314
USP18 deficiency ORPHA:481665
Worster-Drought syndrome ORPHA:3465

Source: Classification of rare neurological diseases according to the Orphanet Database https://www.orpha.net/consor/cgi-bin/Disease_Classif.php?lng=EN&data_id=181&PatId=13024&search=Disease_Classif_Simple&new=1

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Appendix 2

In this section we describe LSDs and neurotransmitter diseases and provide some examples.

Lysosomal storage disorders

LSDs are a group of over 70 diseases characterized by lysosomal dysfunction.[86]

Genes associated with LSDs code lysosomal proteins, including lysosomal enzymes and lysosomal membrane proteins. Defects in lysosome function cause the accumulation of undigested or partially digested macromolecules in lysosomes, which can result in cellular damage.[87] Which protein is affected will determine what symptoms the patient experiences.

"The absence of one or more enzymatic lysosomal enzymes starts a cascade of secondary events, which are most of the time the real cause of all the problems these patients experience," says Professor Scarpa. "Unfortunately, lysosomes are in all the cells of the body, with the exception of the red blood cells, so every kind of organ is hit—the skeleton, the brain, the eyes, the lungs, muscle, the liver and the spleen." The central nervous system is affected in around 60-70% of patients, he adds.

Most LSDs are inherited as autosomal recessive traits,[88] which means two copies of an abnormal gene are required—one from each parent. All individuals carry four or five abnormal genes,[89] so parents who are close relatives (consanguineous) have a higher chance than unrelated parents of carrying the same abnormal gene, which increases the risk of having children with a recessive genetic disorder.

Although individually rare, collectively LSDs affect one in 5,000 people.[90] Their pathogenesis is complex and not completely understood.[91] Onset is usually in infancy and childhood, and most disorders are associated with progressive neurodegenerative symptoms, with symptoms affecting other organs also common.[92]

Lysosomal disorders can be divided into three different types, depending on where undigested macromolecules accumulate and cause symptoms—mostly the muscle, skeleton, or other organs.

Interestingly, in families where more than one person has the same condition, they don't always have the same phenotype. "Even if they share the same genetic mutation, two siblings or even two twins may have different kinds of diseases," says Professor Scarpa.

[86] Platt F M, d'Azzo A, Davidson B L, Neufeld E F, Tifft C J, "Lysosomal storage diseases", *Nat Rev Dis Primers,* 2018 Oct 1;4(1):27, doi: 10.1038/s41572-018-0025-4
[87] Ibid
[88] Ibid
[89] https://rarediseases.org/rare-diseases/lysosomal-storage-disorders/ Accessed 14 September 2021
[90] Platt F M, d'Azzo A, Davidson B L, Neufeld E F, Tifft C J, "Lysosomal storage diseases", *Nat Rev Dis Primers, 2018 Oct 1;4(1):27, doi: 10.1038/s41572-018-0025-4*
[91] Ibid
[92] Ibid

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He suspects this may be due to other genes influencing metabolic pathways, resulting in the accumulation of additional molecules, and/or greater accumulation of substances in specific organs.

Several LSDs can be treated with disease-specific enzyme replacement therapies (for example in Gaucher disease).[93,94] Small-molecule therapies are available for some disorders, including chaperone therapies, which bind to faulty enzymes to stabilise them and enhance their activity in the lysosome (for example, for Fabry disease),[95] as well as substrate reduction therapies.[96] Haematopoietic stem cell transplantation is also an option for some LSDs but must generally be performed early in life for the best outcomes.[97]

Attention has now increasingly turned to gene therapy, which uses viral and non-viral vectors to deliver a functional copy of the defective gene, and genome editing where the patient's genome is manipulated in a controlled manner, for example by inserting a functional copy of a gene at a specific site within the genome.[98,99]

LSDs are good candidates for gene therapy because they are usually related to single defective genes and animal models incorporating these defects have been developed which allow testing of potential treatments.[100] LSDs are particularly amenable to gene therapy treatment, as modified cells can secrete functional enzymes that can make up for defective enzymes in unmodified 'bystander' cells.[101]

[93] Ibid

[94] Massaro G, Geard AF, Liu W, et al, "Gene Therapy for Lysosomal Storage Disorders: Ongoing Studies and Clinical Development", Biomolecules, 2021;11(4):611, Published April 20th 2021, doi:10.3390/biom11040611

[95] Suzuki Y, "Chaperone therapy for molecular pathology in lysosomal diseases", *Brain Dev,* 2021 Jan;43(1):45-54, doi: 10.1016/j.braindev.2020.06.015, Epub 2020 Jul 29. PMID: 32736903

[96] Wheeler S and Sillence D J, "Niemann–Pick type C disease: cellular pathology and pharmacotherapy", *J Neurochem*, 2020, 153: 674-692, https://doi.org/10.1111/jnc.14895

[97] Massaro G, Geard AF, Liu W, et al, "Gene Therapy for Lysosomal Storage Disorders: Ongoing Studies and Clinical Development", *Biomolecules*, 2021;11(4):611, Published April 20th 2021, doi:10.3390/biom11040611

[98] Platt F M, d'Azzo A, Davidson B L, Neufeld E F, Tifft C J, "Lysosomal storage diseases", *Nat Rev Dis Primers*, 2018 Oct 1;4(1):27, doi: 10.1038/s41572-018-0025-4

[99] Massaro G, Geard AF, Liu W, et al, "Gene Therapy for Lysosomal Storage Disorders: Ongoing Studies and Clinical Development", *Biomolecules*, 2021;11(4):611, Published April 20th 2021, doi:10.3390/biom11040611

[100] Ibid

[101] Nagree M S, Scalia S, McKillop W M, Medin J A, "An update on gene therapy for lysosomal storage disorders", *Expert Opin Biol Ther,* 2019 Jul;19(7):655-670, doi: 10.1080/14712598.2019.1607837, Epub 2019 May 6, PMID: 31056978

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Routes of administration for gene therapy

Ex-vivo gene therapy: Also known as haematopoietic stem cell gene therapy (HSC-GT). An advantage of HSC-GT is the ability to perform autologous transplantation (using a patient's own stem cells), which bypasses the risk of graft-versus-host disease that exists with allogeneic HSCT (use of donor stem cells). The gene therapy is administered to haematopoietic stem cells harvested from the patient which are then transplanted back into the patient.

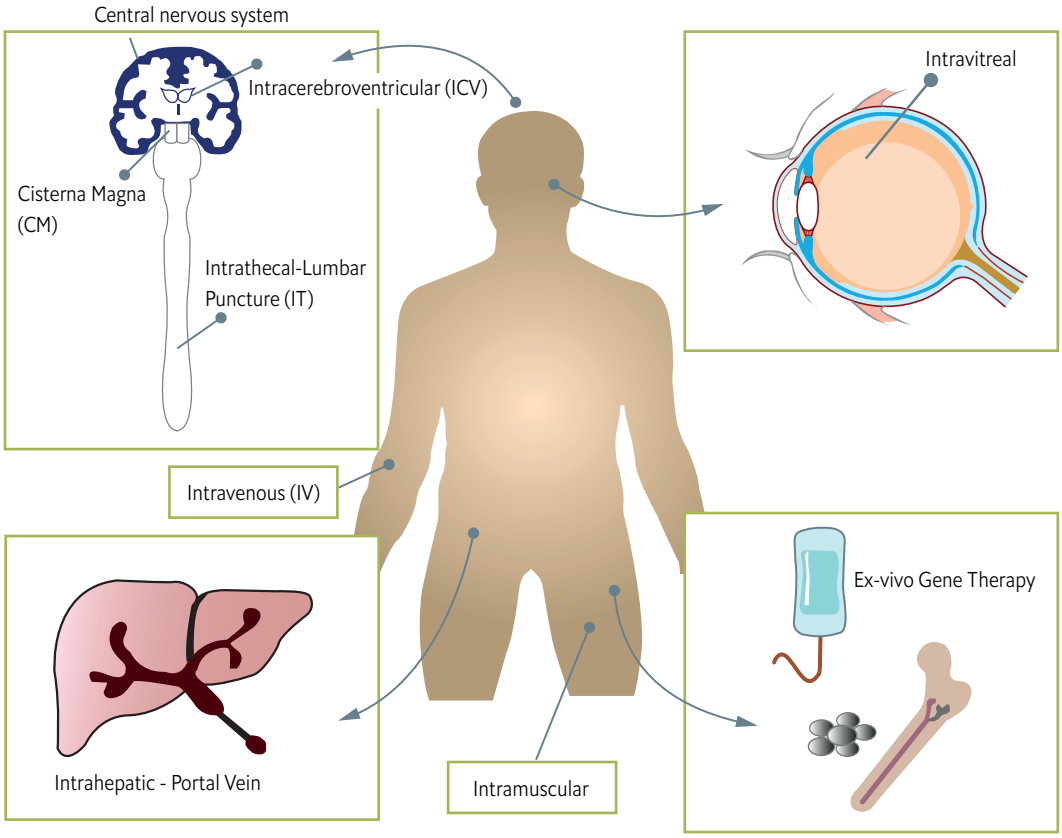
Intra-hepatic portal vein: The selective targeting of organs in order to produce and secrete therapeutic proteins into the bloodstream is an attractive approach to treat systemic diseases. Highly vascularised organs, such as the liver or the lungs, are targets.

Intravitreal: This could be a successful route for targeting a gene therapy for the lysosomal storage disease Batten disease which is characterised by severe and progressive degeneration of the retina.

Intravenous: This requires large batches of vector which is more costly

Central nervous system (Intracerebroventricular, cisterna magna, intrathecal, intraparenchymal) for targeting cells behind the blood-brain barrier.

Intramuscular delivery is minimally invasive yet effective for targeting peripheral nerves.



Sources: Adapted from: Massaro G, Geard AF, Liu W, et al. Gene Therapy for Lysosomal Storage Disorders: Ongoing Studies and Clinical Development. Biomolecules. 2021;11(4):611. Published 2021 Apr 20. doi:10.3390/biom11040611; Tosolini AP, Sleigh JN. Intramuscular Delivery of Gene Therapy for Targeting the Nervous System. Front Mol Neurosci. 2020 Jul 17;13:129.

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Neurotransmitter diseases

Neurotransmitter diseases are a group of rare disorders characterised by defects in the synthesis, degradation or transport of one or more neurotransmitters, or by defects in the synthesis of cofactors, which result in a variety of neurological and neuromuscular symptoms.[102] The disorders are differentiated by which neurotransmitter is affected and how.[103]

Neurotransmitters are chemical messengers that cross the gap between two neurons. Some neurotransmitters have inhibitory effects on the neuron while others excite it.[104] Other neurotransmitters are known as neuromodulators because they affect large numbers of neurons at the same time.[105]

Neurotransmitters can be grouped into:[106]

- Amino acid transmitters including glycine, glutamate and ʟ-aminobutyric acid (GABA).
- Monoamines/biogenic amine transmitters including catecholamines norepinephrine, epinephrine, and dopamine, as well as serotonin. Tetrahydrobiopterin (BH4) is important for the synthesis of these.[107]
- Neuropeptides, classified as short proteins or polypeptides (for example, oxytocin and vasopressin).

When there is a disruption within the neurotransmitter system, it can impact many of the brain's functions, including movement, behaviour and temperature regulation. As a result, symptoms of rare neurotransmitter disorders can be diverse, ranging from severe development delay and unusual movement to excessive sweating and unusual eye movements.[108]

When a child is born with a defect that affects a neurotransmitter, the repercussions can be severe and immediate. The specific symptoms vary according to which neurotransmitter is affected and how. (See examples of conditions below.)

Diagnosis of a neurotransmitter disorder requires assessing neurotransmitter levels in the cerebrospinal fluid, because assessment of peripheral markers in the blood or urine is less reliable.[109]

Like LSDs, most neurotransmitter disorders are inherited in an autosomal-recessive fashion.

Rare neurotransmitter disorders are usually treated by supplementation of missing neurotransmitter precursors or deficient cofactors to support enzyme synthesis.[110] When this is undertaken early in life, it enables, in some cases, significant improvement of motor and cognitive function.[111]

[102] Brennenstuhl H, Jung-Klawitter S, Assmann B, Opladen T, "Inherited Disorders of Neurotransmitters: Classification and Practical Approaches for Diagnosis and Treatment. Neuropediatrics", 2019 Feb;50(1):2-14, doi: 10.1055/s-0038-1673630, Epub 2018 Oct 29, PMID: 30372766

[103] https://rarediseases.org/rare-diseases/tyrosine-hydroxylase-deficiency/ Accessed September 16th 2021

[104] https://www.simplypsychology.org/neurotransmitter.html Accessed September 16th 2021

[105] Ibid

[106] Brennenstuhl H, Jung-Klawitter S, Assmann B, Opladen T, "Inherited Disorders of Neurotransmitters: Classification and Practical Approaches for Diagnosis and Treatment. Neuropediatrics", 2019 Feb;50(1):2-14, doi: 10.1055/s-0038-1673630, Epub 2018 Oct 29, PMID: 30372766

[107] Opladen T, López-Laso E, Cortès-Saladelafont E. et al. Consensus guideline for the diagnosis and treatment of tetrahydrobiopterin (BH4) deficiencies. Orphanet J Rare Dis 15, 126 (2020). https://doi.org/10.1186/s13023-020-01379-8

[108] http://pndassoc.org/diseases/pnd.html Accessed September 2021

[109] Brennenstuhl H, Jung-Klawitter S, Assmann B, Opladen T, "Inherited Disorders of Neurotransmitters: Classification and Practical Approaches for Diagnosis and Treatment. Neuropediatrics", 2019 Feb;50(1):2-14, doi: 10.1055/s-0038-1673630, Epub 2018 Oct 29, PMID: 30372766

[110] Ibid

[111] Opladen T, López-Laso E, Cortès-Saladelafont E, Pearson T S, Sivri H S, Yildiz Y, Assmann B, Kurian M A, Leuzzi V, Heales S, Pope S, Porta F, García-Cazorla A, Honzík T, Pons R, Regal L, Goez H, Artuch R, Hoffmann GF, Horvath G, Thöny B, Scholl-Bürgi S, Burlina A, Verbeek M M, Mastrangelo M, Friedman J, Wassenberg T, Jeltsch K, Kulhánek J, Kuseyri Hübschmann O, International Working Group on Neurotransmitter related Disorders (iNTD), "Consensus guideline for the diagnosis and treatment of tetrahydrobiopterin (BH4) deficiencies", *Orphanet J Rare Dis, 2020 May 26;15(1):126. doi: 10.1186/s13023-020-01379-8, Erratum in: Orphanet J Rare Dis, 2020 Aug 5;15(1):202, PMID: 32456656; PMCID: PMC7251883*

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Existing treatments are able to completely resolve the symptoms of some paediatric neurotransmitter disorders, and improve quality of life for children with others.[112] Gene therapies that address deficiencies in the neurotransmitter pathways to boost neurotransmitter levels are under investigation and have the potential to provide life-changing or transformational benefits without the need for lifelong treatment.[113]

Developing an effective gene therapy for a neurotransmitter disorder is particularly challenging, says Ms Ríos Aroca. The therapy would need to reach a large proportion of the affected neurons, and neurons are difficult to target because they do not replicate in the same way as other cells and a large proportion of those affected are often behind the blood-brain barrier.[114]

How children are affected by some rare neurological disorders

Lysosomal storage disorders

Cystinosis

Cystinosis is a rare genetic disorder associated with the build-up of an amino acid called cystine in different tissues and organs, most commonly the kidneys and eyes, but also muscles, liver, pancreas and brain. It is estimated to occur in 1 in 100,000-200,000 people. There are three types and nephropathic cystinosis is the most common and severe form, and early detection and treatment are critical in slowing progression. Symptoms, such as growth failure and renal Fanconi syndrome, may appear from infancy and usually by the age of one. On average, untreated children will grow at 60% of the expected rate.

Niemann-Pick disease

Niemann-Pick disease is a group of inherited metabolic disorders in which harmful quantities of lipids accumulate in the brain, spleen, liver, lungs and bone marrow. It is divided into four types according to the gene and the signs and symptoms: type A, type B, type C1 and type C2. Other rarer types have been described. Types A and B are estimated to affect 1 in 250,000 individuals. Type A occurs particularly frequently among people from the Ashkenazi community, where incidence is around 1 in 40,000 individuals. Combined, types C1 and C2 affect around 1 in 150,000 individuals; however, type C1 is more common, making up 95% of cases. Symptoms may include lack of muscle co-ordination, brain degeneration, learning problems and an enlarged liver and spleen.

Pompe disease

Pompe disease is a condition in which glycogen accumulates in a variety of tissues, but primarily in skeletal, smooth and cardiac muscle. Incidence is around 1 in 40,000 births. Symptoms can occur at any age, and earlier onset is associated with faster progression and greater severity. The most severely affected generally present within the first three months of life with heart problems and skeletal muscle weakness and have a life expectancy of less than two years. Other characteristic symptoms include a large tongue, a moderate enlargement of the liver, and legs that rest in a frog-like position. Affected children have problems feeding, respiratory difficulties and major developmental milestones are either delayed or not reached. Mental development is usually normal but almost all infants experience hearing loss.

[112] http://pndassoc.org/diseases/pnd.html Accessed September 21st 2021

[113] Hwu P W, Kiening K, Anselm I et al, *EMBO Mol Med*, 2021;13(9):e14712, doi:10.15252/emmm.202114712

[114] Ibid

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Neurotransmitter disorders

Aromatic L-amino acid decarboxylase (AADC) deficiency

This condition is related to decreased activity of aromatic L-amino acid decarboxylase, an enzyme involved in the synthesis of neurotransmitters. Symptoms appear during the first few months of life. It is extremely rare. Fewer than 150 patients have been reported in the literature. The estimated prevalence in the US is roughly 1-3:100,000 of newborns. The two most common early symptoms are decreased muscle tone in the trunk and abnormal eye movements, but other movement disorders can be present, such as decreased movements and involuntary writhing movements, and these may be accompanied by severe developmental delay, restricted growth, and disruption of unconscious body functions. Many affected children do not reach adulthood, but some with milder disease do.

Tyrosine hydroxylase deficiency

Tyrosine hydroxylase deficiency results in a deficiency of dopamine, which is critical for certain brain processes, especially around movement. The disease can present as a wide spectrum ranging from a mild movement disorder to a life-threatening, neurological disorder in its most severe form. The severe form causes symptoms from the first months of life. Fewer than 50 cases have been reported, so the exact incidence is unknown. The most common symptoms include a clumsy manner of walking and involuntary muscle contractions that force the body into abnormal, sometimes painful, movements. Additional symptoms include eye abnormalities and a tendency of affected children to walk on their tiptoes.

Succinic semialdehyde dehydrogenase (SSADH) deficiency

This disease disrupts the metabolism of the inhibitory neurotransmitter gamma-aminobutyric acid leading to the abnormal accumulation of succinic semialdehyde. Over 400 cases have been identified, but due to the diverse and nonspecific nature of symptoms, experts believe it is significantly underdiagnosed. It is usually diagnosed in infancy or childhood, and most of those affected will experience mild to severe intellectual disability, as well as delays in the acquisition of skills requiring the co-ordination of mental and physical activities, and delays in speech development. Some people may have an impaired ability to co-ordinate voluntary movements, seizures, and/or behavioural abnormalities.

Acknowledgement: The section on sample diseases has been adapted from the websites of the National Organization for Rare Diseases' Rare Disease Database, National Institutes of Health's US National Library of Medicine Medline Plus, and National Center for Advancing and Translational Sciences' Genetics and Rare Diseases Information Centre, and Massaro G, Geard A F, Liu W, et al, "Gene Therapy for Lysosomal Storage Disorders: Ongoing Studies and Clinical Development", *Biomolecules*, 2021;11(4):611, Published April 20th 2021, doi:10.3390/biom11040611

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