Rare diseases: still on the fringes of universal health coverage in Europe

Birutė Tumienė,[a,b,*] Augutė Juozapavičiūtė,[a,b,c] and Vytenis Andriukaitis[d]

[a]Faculty of Medicine, Institute of Biomedical Sciences, Vilnius University, M. K. Ciurlionio str. 21, Vilnius LT-03101, Lithuania
[b]Vilnius University Hospital Santaros Klinikos, Rare Diseases Coordination Center, Santariskiu str. 2, Vilnius LT-08661, Lithuania
[c]Faculty of Medicine, Institute of Clinical Medicine, Vilnius University, M. K. Ciurlionio str. 21, Vilnius LT-03101, Lithuania
[d]European Institute of Health and Sustainable Development, Petro Vileisio str. 18A - 301, Vilnius LT-10306, Lithuania

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Summary

Despite general advancements in population health indicators and universal health coverage, people living with rare diseases and their families still experience considerable unmet needs, including prolonged diagnostic journeys, limited treatment options, and a huge psychosocial burden due to the lack of coordinated, integrated care. Attainment of universal health coverage for rare diseases is dependent on fundamentally different health determinants and demands for different solutions. This involves consolidating expertise through Centers of Excellence, establishing efficient care pathways, fostering extensive collaboration at European and global levels in research and healthcare, and putting patients at the center of care. Furthermore, development of specific indicators and coding systems is crucial for monitoring progress. Only in this way Europe can strive towards a future where people living with rare diseases receive the same level of equitable, safe, high-quality healthcare as other members of the society, in alignment with the overarching goal of leaving no one behind.

Keywords: Rare disease; Healthcare policy; Universal health coverage; Health determinants; National frameworks; Care pathways; European reference networks

Introduction: unmet needs of people living with rare diseases and their families

In 2015, 193 Member States of the United Nations (UN) agreed on the Sustainable Development Goals (SDGs) and set out an ambitious agenda by 2030.[1] Universal health coverage (UHC) embodies the 2030 Agenda's pledge to ensure everyone's equitable access to needed healthcare services of sufficient quality without suffering financial hardship. The catchphrase of the SDGs—leaving no one behind—finds its way into the main global and European policy agendas, including UHC2030 movement,[2] Triple Billion Targets of WHO's Thirteenth General Programme of Work,[3] Roadmap to implement the 2030 Agenda for Sustainable Development, adopted by WHO's regional Office for Europe[4] and the new vision for WHO's European Region (Box 1).[5]

Countries continuously measure their progress towards UHC using agreed health indicators[6] and try to identify the key health determinants which influence health status and determine health differentials or health inequalities.[7] Health authorities and politicians shape their policies and reforms to address these determinants, traditionally according to the WHO's UHC Cube Diagram.[8] Claims that European high-income countries provide almost universal access to high quality healthcare already for decades are widespread. These claims are usually supported by ever improving health indicators–increasing life expectancy, decreasing infant and maternal mortality and diminishing incidence of communicable diseases.[9] However, some of our population groups escape these monitoring frameworks and stay on the fringes of universal health coverage. Lack of proper coding and tracebility in healthcare systems preclude collection of data for rare diseases, therefore, they usually remain invisible.[10] Consequently, while common diseases such as cancer or chronic non-communicable diseases pave their ways to health policies and are prioritized for healthcare system reforms and research funding, rare diseases are frequently left behind.

In 2019, United Nations declared that rare diseases are among the most vulnerable groups,[11] and in 2021 a UN Resolution "Addressing the challenges of persons living with a rare disease and their families" was adopted.[12] Indeed, despite the fact that people living with rare diseases (PLWRD) comprise a significant proportion of our societies—up to 5.9%, excluding rare cancers, infectious diseases and intoxications, which equates to 17.8–30.3 million affected people in the European Union at any point in time[13]—they still experience

*Corresponding author. Faculty of Medicine, Department of Human and Medical Genetics, Institute of Biomedical Sciences, Vilnius University, Santariskiu str.2, Vilnius LT-08661, Lithuania.
E-mail address: birute.tumiene@santa.lt (B. Tumienė).

Box 1.

Key messages and recommendations.

- People living with rare diseases (PLWRD) still experience considerable unmet needs in diagnostics, treatment and long-term management and stay on the fringes of universal health coverage (UHC) in Europe.
- Health determinants for universal health coverage in rare diseases fundamentally differ from those applicable to common diseases.
- Strategies to reduce inequalities of UHC for PLWRD should target rare disease-specific health determinants.

numerous unmet needs. Even in the most developed high-income countries, the diagnostic odyssey of a patient with a rare disease takes on average five to six years. During this time, the patient's health often deteriorates, complications develop and fatal outcomes may even occur without receiving a diagnosis.[14] PLWRD and their families experience enormous challenges in this odyssey, navigating health systems among various healthcare providers and facilities; it induces huge psychosocial burden and diminishes trust in healthcare systems.[15,16] After the appearance of the first symptoms of the disease, healthcare workforce at the usual entry points to healthcare systems are not prepared to recognize "red flags" of possible rare diseases and to refer for specialized diagnostics: they lack education and even awareness on rare diseases and healthcare system literacy for referrals to Centers of Expertise for rare diseases, therefore, PLWRD often get "stuck" in healthcare systems.[17] Furthermore, a large number of rare diseases are currently impossible to diagnose, even through the usage of all available diagnostic measures in clinical practice, as their etiology has not yet been determined[18]; on average, 300 novel rare diseases are being described each year, therefore, a large part of PLWRD live with an undiagnosed disease and suffer an even greater burden of uncertainty.[19]

Once the disease is diagnosed, effective treatments should be instituted. Only 5% of rare diseases have effective specific treatments that may change the course of a disease and substantially improve outcomes and quality of life for patients and their families.[20] Unfortunately, Orphan drugs are not only scarce, but also very expensive and their accessibility is far from universal, with major inequities across and within countries.[21] The availability of medicines for children is particularly limited: even existing medicines are often not adapted for children, and the necessary clinical trials to investigate their safety and effectiveness in this population have not been carried out.[22] The path to effective treatments is the same for both rare and common diseases—that is, we need to unveil the mechanisms of a given disease, find out biological targets for treatments, and develop drugs. However, the very first step towards the development of medicines—elucidation of pathological mechanisms—has been taken in only about 1.000 of all (up to 8.000) rare diseases.[23] The necessary research infrastructures are also missing, as patient registries for natural disease course studies or collection of cohorts for clinical studies, and biobanks are lacking for most conditions.[24] For this reason, for most of the remaining 7.000 rare diseases, specific treatments are not even on the horizon, with some rare diseases appearing currently "undruggable" (like chromosomal disorders).

It is true that some common diseases also lack effective treatments to address their root causes. In such cases, efficient healthcare systems propose an alternative–effective symptomatic treatments and integrated care to alleviate or prevent complications, slow down the progression of the disease, and improve the quality of life of patients and their families. In rare diseases, there are almost no evidence-based resources (i.e., clinical practice guidelines) for the organization of care pathways to ensure appropriate navigation of patients, their data and funds across systems.[25] While approximately 70% of rare diseases are of childhood onset, induce disabilities and complex needs and are often lifelong, fragmented by medical specialties and focused on treating acute episodes healthcare systems fail to provide the necessary integrated, multidisciplinary expert care. The weakest point in the care chain is management of a wide range of disease course-related transitions (e.g, transitions across highly-specialized and local healthcare services[26] or transition to palliative care),[27] age-related transitions (e.g. transition from childhood to adult services[28] or challenges related to pregnancy and ageing),[29] and effective intersectoral collaboration (e.g. with social and educational sectors).[30] Unpreparedness of our care systems to provide safe, high-quality and coordinated care for PLWRD places a heavy burden on patients and their families: 7 out of 10 patients or their caregivers have to reduce or stop their professional activities.[31] Due to all these challenges PLWRD and their caregivers are frequently among the most unfortunate members of our society: many of them experience depression and anxiety,[16,32] carers even report that the burden of organising care has a greater negative impact on their mental health than the diagnosis of a rare, incurable illness.[15,33]

Moreover, some patients experience a double blow: not only nosological inequities, but also geographical; e.g., it was found that the outcomes of rare cancers are much worse compared to the corresponding common cancers, but in some, mainly EU-13 countries (i.e. countries that joined the EU after 2004), these outcomes are considerably worse than those in the old EU members.[34] Furthermore, EU-13 countries have a greater lack of diagnostics (e.g. universal newborn screening covers fewer diseases,[35] there is a lack of genetic diagnostic services),[36] less funding for long-term care,[37] in long-term conditions a higher burden of care lies on the shoulders of patients' relatives.[38]

In this publication we will discuss what are the main health determinants for UHC in rare diseases and will provide some proposals on solutions that could be taken to tackle these health determinants.

Health determinants for universal health coverage in rare diseases

The first step to reduce roadblocks towards the full universal health coverage Cube[20] for rare diseases is to identify the root causes, i.e., to answer the questions "Why is there a difference between rare and common diseases in terms of UHC? Which health determinants should we tackle to bridge these differences?" **Health determinants** are factors which influence health status and determine health differentials or health inequalities. These are many and varied, including biological/genetic, environmental, behavioural, socioeconomic, healthcare and political/legal factors. Importantly, health determinants for rare diseases fundamentally differ from those for common diseases. At least 72% of rare diseases have a genetic basis, i.e., they are subject to non-reducible biological or **genetic determinants**.[13] Therefore, rare diseases affect people of all social and economic backgrounds much more equally as compared to common diseases. Although socio-economic factors are highly important, they are rather a consequence than a cause of rare diseases: families frequently face financial difficulties not before the disease onset, as in the case of common chronic non-infectious diseases, but afterwards, mostly as a consequence of catastrophic health expenditures due to non-reimbursable Orphan drugs or diminished professional activities while caring for patients with disabilities and complex needs.[39] In the field of rare diseases, factors related to the political will to devote sufficient attention to this important public health problem and the organization of care are the most important. **Healthcare system determinants** relate to the healthcare services for timely diagnostics, safe and high-quality care and long-term management of rare diseases and require completely different solutions than those for common diseases; these solutions can even contradict the current trends for healthcare system reforms, e.g., concentration of services in primary care level.[40] Not only healthcare workforce planning is very important (development of highly-specialized rare disease experts takes even longer than development of usual healthcare workforce, therefore the problem of workforce shortage is very relevant in rare diseases), but also the equipment of existing and future healthcare specialists with the necessary knowledge and skills to deal with the specific challenges of rare diseases.[17] Appropriate political will to apply organizational and legal/regulatory measures are necessary for these changes, therefore, **political and legal determinants** play a key role. Unfortunately, despite high unmet needs, rare diseases still remain at the outskirts of political agendas in many European countries. No country can individually solve all the challenges related to rare diseases, therefore a wide-scale cooperation is necessary, including both cross-border healthcare[41] and European collaboration in rare disease research.[24] Finally, **commercial determinants** in rare diseases were mostly shaped by Orphan drug policies: although Regulation (EC/141/2000) on Orphan Medicinal Products in the EU[42] resulted in the availability of numerous Orphan drugs that were non-existent before, accessibility to these drugs is still highly unequal and an issue even in wealthy countries and the benefits of Orphan drug Regulation were significantly overshadowed by commercial profit-making behaviour.[22,43]

Answers to the question "Why?" (i.e. identification of specific health determinants for UHC in rare diseases) may give us clues to the questions "What?" and "How?" (i.e., possibilities to identify solutions to tackle these determinants and increase UHC for rare diseases). A roadmap towards UHC for rare diseases involves management of all relevant health determinants and some of the solutions provided below are already being taken.

Towards universal health coverage for rare diseases

Solutions to tackle healthcare system determinants

Organization of care services for PLWRD and their families fundamentally differ as compared to common diseases. Rare disease experts are as scarce as PLWRD, therefore, centralization of this expertise in Centers of Excellence (CoE) is of enormous importance. Over several decades, CoE for rare and complex diseases were established in all Member States across Europe and this process was especially fueled by the establishment of the European Reference Networks (ERNs).[44] At the same time, Resource centers were set up in many countries as a one-stop-shop service for integrated care and case management, providing holistic approach and support to PLWRD, their families and professionals.[31] Establishment of clear care pathways among these centers and local care providers may provide means for timely diagnostics and long-term integrated care. Appropriate balance between centralized, highly-specialized services and those that may safely and with sufficient quality be provided locally (along with appropriate guidance, data sharing and communication between CoE and local providers) may alleviate burden of travelling and even "exile due to illness".[26] Although there is still a lack of data, Member States can be encouraged to organize appropriate services in an efficient, cost-effective and rational way through economic arguments: complex trajectories of rare disease patients in healthcare systems and active, frequently lifelong usage of services provide many risks for ineffective and even wasteful care.[45,46] As healthcare systems become increasingly pressured by rising costs and demands, tackling wasteful spending in rare diseases is of ever increasing importance.

Solutions to tackle political and legal determinants

The first step to create a framework for coherent, coordinated actions in rare disease field that brings together multistakeholder communities for common goals and ensures responsibility sharing is adoption of a National rare disease Plan or Strategy (NP/NS). Starting with the first French National Plan for Rare Diseases 2005–2008[47] and strongly stimulated by the EUROPLAN project,[48] the NP/NS development process gradually covered almost the entire EU; currently, 28 EU and EEA Member States (except from Malta and Sweden) have adopted NP/NS for rare diseases. Unfortunately, many of these plans remain more an expression of a good will than a coherent political tool to induce important reforms and reorganizations. Specific goals of NP/NS are frequently unsupported by funding, there is a lack of NP/NS sustainability and intersectoral collaboration.[49] Political and legal measures are also important for the implementation and regulation of other healthcare aspects, e.g. designation of CoEs and establishment of care pathways. The need to centralize experience and resources in CoEs may become a sensitive political issue: although many healthcare providers may have ambitions to put a logo of a CoE next to its name, the only way to ensure safe and high-quality highly-specialized services for PLWRD is through centralization, therefore, designation of limited number of CoEs out of many potential candidate healthcare providers may be associated with tough political decisions.[50]

European and global cooperation in both cross-border healthcare and research is another key area for policy actions. Although Directive 2011/24/EU on the application of patients' rights in cross-border healthcare[51] has created a legal basis for the application of cross-border healthcare among all EU Member States, the volume of cross-border services remains low,[52] and one of the main reasons could be willingness of Member States to retain their autonomy and subsidiarity in healthcare as enshrined in the article 168 of the Treaty on the Functioning of the European Union (TFEU). However, the principle of subsidiarity refers in general to the choice of the most suitable and efficient level for taking policy action, and in the case of rare diseases this level may be at the EU rather than at the national level.[53] Luckily, the 2011 Directive also defined the principles for the establishment and governance of ERNs, which bring together CoEs for rare and complex diseases. Launched in 2017, ERNs revealed the true extent of rare disease prevalence and the need for European cooperation in the field of rare diseases: after the first call for Full Members, 24 ERNs united >900 CoEs in 26 EU countries, and after the second call ERNs encompass >1400 CoEs dispersed across the whole EU.[44] This unprecedented and far-reaching pioneer initiative provides a great potential to bring the highest quality healthcare closer to every EU citizen's home, most frequently through "expertise goes first, not the patient" approach when complex cases are first discussed in the safe, privacy and data protection preserving platform (so-called Clinical Patient Management System, CPMS).[54] Such an approach not only provides the "doors" to ERNs, but also ensures gatekeeping function (only those patients for whom it is impossible to provide the necessary services in the national healthcare system experience physical cross-border healthcare). Besides, through joining resources and expertise, ERNs provide economies of scale, scope and time for Member States in terms of rare disease research, clinical trials, development of clinical practice guidelines, educational programmes and other important activities. Finally, ERNs may reduce not only nosological, but also geographical inequities: Affiliated Partnership provides the opportunities to join ERNs to centers in countries that lack sufficient competences and do not meet the strict criteria for ERN Full Membership. Unfortunately, the delegation of centers to ERNs also requires some political will and current ERN coverage is still quite uneven across the EU: there are still some "whitish gaps" on the EU map, therefore, the "doors" to each ERN cannot be guaranteed for citizens of these countries.[44] Another, perhaps one of the most important challenges of ERNs, also mentioned in the evaluation by the European Court of Auditors[55] and other documents, is insufficient integration of ERNs into national systems. The basic units of ERNs—CoE for rare and complex diseases—operate in their own countries and are dependent on the existing national or even regional legal and organizational frameworks. ERN integration provides the means for both ERN sustainability and reaping their full benefits for Member States, but requires certain legal and organizational solutions at the national or even regional level, which would ensure opportunities to carry out European-wide ERN activities.[44] Currently, very important steps are being taken to solve this problem: in 2017, the working group established in the ERN Board of Member States defined the most important areas of interventions, and the Joint Action (JA) starting in 2024 will hopefully ensure a deeper assessment of the current situation, exchange of best practices among Member States and identification of solutions for evidence-based policy-making.

EU-wide and global collaboration is no less important in rare disease research: in 2019, a mission-like research and innovation program–the European Joint Program on Rare Diseases (EJPRD)–was launched.[56] The four pillars of this program not only provide funding for high-quality international rare disease research, but also create a comprehensive ecosystem of science and its policies, research infrastructures, education and translation into clinical practice. Eventually EJPRD creates a lively community with common goals, language and standards, and provides a smooth innovation cycle "from bed to bench and back again". This programme follows the vision established by the

International Rare Disease Research Consortium (IRDiRC): "Enable all people living with a rare disease to receive an accurate diagnosis, care, and available therapy within one year of coming to medical attention".[57] European Rare disease research Coordination and support Action Consortium (ERICA) aims to coordinate the clinical research activities of the European Reference Networks, and the European Platform on Rare Disease Registration (EU RD Platform) copes with the fragmentation of rare disease patients data contained in hundreds of registries across Europe.[58] The Rare Disease Partnership that is currently under development has the potential to further strengthen and expand the scopes and impacts of rare disease research over the period of 2024–2030; again, the willingness of individual countries and the EC to participate and to allocate sufficient resources to these rare disease research programmes is crucial.

Finally, a real basis for responding unmet patient needs is through patient-centredness in both healthcare and research. This process requires political and legal measures to ensure the inclusion and participation of patients and their representatives in all relevant processes, establishment of partnerships and the means to reinforce their voice and advocacy.[59] Such measures are applied in ERNs through the establishment of European Patient Advocacy Groups (ePAGs).[60]

Appropriate monitoring is necessary to evaluate the current situation and to measure progress in UHC for rare diseases. Unfortunately, rare diseases are mostly not reflected in the usual disease codification systems, as ICD-10. Although specific rare disease codification system–ORPHA coding—was developed by Orphanet, only several EU countries adopted ORPHA coding in their national healthcare systems.[10] Importantly, rare diseases are also left out of the scope in the assessments of UHC as there are no specific indicators for rare diseases.[40] Establishment of rare disease-specific indicators for UHC and implementation of ORPHA codification may enable assessment, monitoring and benchmarking across and within countries.

Solutions to tackle commercial determinants

Regulation (EC/141/2000) on Orphan Medicinal Products in the EU[42] was adopted in 2000 and resulted in more than 150 Orphan drugs in market as of today, compared to just eight therapies for rare diseases available before 2000.[22] While Regulation did provide a strong impetus in the beginning, profit-making and burdens of excessive risk have severely hampered pharmacy-driven innovation subsequently and, according to the recent evaluation, it was not sufficient to direct the development in the areas of greatest unmet needs. Moreover, accessibility of existing Orphan drugs is a huge issue, as rising costs become unbearable even for wealthy countries.[61,62] Incentivization of research infrastructures and public-private partnerships to combat a "valley of death" between fundamental academic research and translation into clinical practice,[63] clinical trial designs for small population studies,[64] academia-driven clinical studies and drug repurposing,[65] change of incentives and regulations for Orphan drugs[22] and some other measures are being discussed as possible solutions.

These measures, together with the solutions mentioned above to address healthcare system and political/legal determinants, may also reduce the impact of socio-economic determinants on PLWRD and their families (such as catastrophic expenditures and the need to reduce professional activities for caregiving). Although genetic determinants are (largely) non reducible (except for genetic therapies which are already being implemented and many more are expected to appear in the near future),[23] organization of appropriate genetic services, including the availability of genetic diagnostics and prevention[36] and the measures to increase genetic literacy among healthcare workforce[66] may reduce the burden of genetic diseases on PLWRD, their families and society.

Search strategy and selection criteria

References for this personal view were identified through searches of the authors' own files and from searches of PubMed with the search terms "rare disease" AND "healthcare system", "health determinants", "universal health coverage", and "European Reference Networks". Only papers published in English were reviewed. The final reference list was generated on the basis of relevance to the scope of this manuscript. We acknowledge limitations mostly due to systemic lack of information on health determinants in UHC for PLWRD.

Conclusion

In conclusion, this publication highlights the urgency to address the unmet needs of PLWRD and their families in Europe through tackling specific health determinants. While considerable progress has been made in both healthcare and research, further action is required at both national and European levels. Only in this way Europe can strive towards a future where people living with rare diseases receive the same level of equitable, safe, high-quality healthcare as other members of the society, in alignment with the overarching goal of leaving no one behind.

Contributors

BT and VA developed the idea for the manuscript. All authors contributed to the structure and development of the paper. BT conducted the literature review and drafted the manuscript. All authors critically revised the manuscript for content and approved the final version. All authors endorse full responsibility for the content.

Declaration of interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no other competing interests.

References

1 UN general assembly, transforming our world: the 2030 agenda for sustainable development, 21 October 2015, A/RES/70/1. Available at: https://www.refworld.org/docid/57b6e3e44.html.
2 UHC2030. Key asks from the UHC movement. Available at: https://www.uhc2030.org/fileadmin/uploads/uhc2030/Documents/UN_HLM/UHC_Key_Asks_final.pdf.
3 *WHO. 13th general programme of work (GPW13)*. World Health Organization; 2019. Available at: https://www.who.int/publications/i/item/thirteenth-general-programme-of-work-2019-2023.
4 World Health Organization Regional Office for Europe. *Roadmap to implement the 2030 agenda for sustainable development, building on health 2020, the European policy for health and well-being*. Copenhagen: World Health Organization Regional Office for Europe; 2017. Available at: http://www.euro.who.int/__data/assets/pdf_file/0008/345599/67wd09e_SDGroadmap_170638.pdf.
5 Kluge H. A new vision for WHO's European Region: united action for better health. *Lancet Public Health*. 2020;5(3):e133–e134. https://doi.org/10.1016/S2468-2667(20)30003-7.
6 Working Group for Monitoring Action on the Social Determinants of Health. Towards a global monitoring system for implementing the Rio Political Declaration on Social Determinants of Health: developing a core set of indicators for government action on the social determinants of health to improve health equity. *Int J Equity Health*. 2018;17(1):136. https://doi.org/10.1186/s12939-018-0836-7. PMID: 30185200; PMCID: PMC6126010.
7 Marmot M, Allen J, Bell R, Bloomer E, Goldblatt P. Consortium for the European review of social determinants of health and the health divide. WHO European review of social determinants of health and the health divide. *Lancet*. 2012;380(9846):1011–1029. https://doi.org/10.1016/S0140-6736(12)61228-8. Epub 2012 Sep 8. PMID: 22964159.
8 Roberts MJ, Hsiao WC, Reich MR. Disaggregating the universal coverage cube: putting equity in the picture. *Health Syst Reform*. 2015 Jan 2;1(1):22–27. https://doi.org/10.1080/23288604.2014.995981. PMID: 31519090.
9 GBD 2017 Mortality Collaborators. Global, regional, and national age-sex-specific mortality and life expectancy, 1950-2017: a systematic analysis for the global burden of disease study 2017. *Lancet*. 2018;392(10159):1684–1735. https://doi.org/10.1016/S0140-6736(18)31891-9. Epub 2018 Nov 8. Erratum in: Lancet. 2019 Jun 22;393(10190):e44. PMID: 30496102; PMCID: PMC6227504.
10 Mazzucato M, Pozza LVD, Facchin P, et al. ORPHAcodes use for the coding of rare diseases: comparison of the accuracy and cross country comparability. *Orphanet J Rare Dis*. 2023;18(1):267. https://doi.org/10.1186/s13023-023-02864-6. PMID: 37667299; PMCID: PMC10476382.
11 UN. Political declaration of the high-level meeting on universal health coverage: universal health coverage: moving together to build a healthier world. Available at: http://www.un.org/pga/73/wp-content/uploads/sites/53/2019/07/FINAL-draft-UHCPolitical-Declaration.pdf; 2019.
12 United Nations. Resolution adopted by the general assembly on 16 December 2021 76/132. In: *Addressing the challenges of persons living with a rare disease and their families*; 2021. Available online: https://digitallibrary.un.org/record/3953765?ln=en.
13 Nguengang Wakap S, Lambert DM, Olry A, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. *Eur J Hum Genet*. 2020;28(2):165–173. https://doi.org/10.1038/s41431-019-0508-0.
14 Taruscio D, Floridia G, Salvatore M, Groft SC, Gahl WA. Undiagnosed diseases: Italy-US collaboration and international Efforts to tackle rare and common diseases lacking a diagnosis. *Adv Exp Med Biol*. 2017;1031:25–38. https://doi.org/10.1007/978-3-319-67144-4_2.
15 Currie G, Szabo J. "It is like a jungle gym, and everything is under construction": the parent's perspective of caring for a child with a rare disease. *Child Care Health Dev*. 2019;45(1):96–103. https://doi.org/10.1111/cch.12628. Epub 2018 Nov 8. PMID: 30370696.
16 Bogart KR, Irvin VL. Health-related quality of life among adults with diverse rare disorders. *Orphanet J Rare Dis*. 2017;12(1):177. https://doi.org/10.1186/s13023-017-0730-1. PMID: 29212508; PMCID: PMC5719717.
17 Tumiene B, Peters H, Melegh B, et al. Rare disease education in Europe and beyond: time to act. *Orphanet J Rare Dis*. 2022;17(1):441. https://doi.org/10.1186/s13023-022-02527-y. PMID: 36536417; PMCID: PMC9761619.
18 Hartley T, Lemire G, Kernohan KD, Howley HE, Adams DR, Boycott KM. New diagnostic approaches for undiagnosed rare genetic diseases. *Annu Rev Genomics Hum Genet*. 2020;21:351–372. https://doi.org/10.1146/annurev-genom-083118-015345. Epub 2020 Apr 13. PMID: 32283948.
19 Aldiss S, Gibson F, Geoghegan S, et al. 'We don't know what tomorrow will bring': parents' experiences of caring for a child with an undiagnosed genetic condition. *Child Care Health Dev*. 2021;47(5):588–596. https://doi.org/10.1111/cch.12866. Epub 2021 Mar 22. PMID: 33709393.
20 Fermaglich LJ, Miller KL. A comprehensive study of the rare diseases and conditions targeted by orphan drug designations and approvals over the forty years of the Orphan Drug Act. *Orphanet J Rare Dis*. 2023;18(1):163. https://doi.org/10.1186/s13023-023-02790-7. PMID: 37353796; PMCID: PMC10290406.
21 Degtiar I. A review of international coverage and pricing strategies for personalized medicine and orphan drugs. *Health Policy*. 2017;121(12):1240–1248. https://doi.org/10.1016/j.healthpol.2017.09.005.
22 *Joint evaluation of regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products {SEC(2020) 291 SWD*. 2020:164.
23 Tambuyzer E, Vandendriessche B, Austin CP, et al. Therapies for rare diseases: therapeutic modalities, progress and challenges ahead. *Nat Rev Drug Discov*. 2020;19(2):93–111.
24 Julkowska D, Austin CP, Cutillo CM, et al. The importance of international collaboration for rare diseases research: a European perspective. *Gene Ther*. 2017;24(9):562–571. https://doi.org/10.1038/gt.2017.29. Epub 2017 Jul 27. PMID: 28440796; PMCID: PMC5628265.
25 Pavan S, Rommel K, Mateo Marquina ME, Höhn S, Lanneau V, Rath A. Clinical practice guidelines for rare diseases: the Orphanet database. *PLoS One*. 2017;12(1):e0170365. https://doi.org/10.1371/journal.pone.0170365. PMID: 28099516; PMCID: PMC5242437.
26 Tumiene B, Graessner H. Rare disease care pathways in the EU: from odysseys and labyrinths towards highways. *J Community Genet*. 2021;12(2):231–239. https://doi.org/10.1007/s12687-021-00520-9. Epub 2021 Mar 18. PMID: 33738760; PMCID: PMC8141079.
27 Adams LS, Miller JL, Grady PA. The spectrum of caregiving in palliative care for serious, advanced, rare diseases: key issues and research directions. *J Palliat Med*. 2016;19(7):698–705. https://doi.org/10.1089/jpm.2015.0464. Epub 2016 Jun 1. PMID: 27249541; PMCID: PMC4931351.
28 Heath G, Farre A, Shaw K. Parenting a child with chronic illness as they transition into adulthood: a systematic review and thematic synthesis of parents' experiences. *Patient Educ Couns*. 2017;100(1):76–92. https://doi.org/10.1016/j.pec.2016.08.011. Epub 2016 Aug 16. PMID: 27693084.
29 Murphy E. Pregnancy in women with inherited metabolic disease. *Obstet Med*. 2015;8(2):61–67. https://doi.org/10.1177/1753495X15576442. Epub 2015 Mar 29. PMID: 27512458; PMCID: PMC4935010.
30 Depping MK, Uhlenbusch N, von Kodolitsch Y, Klose HFE, Mautner V-F, Löwe B. Supportive care needs of patients with rare chronic diseases: multi-method, cross-sectional study. *Orphanet J Rare Dis*. 2021;16(1):44.
31 Castro R, Senecat J, de Chalendar M, Vajda I, Dan D, Boncz B, EURORDIS Social Policy Advisory Group. Bridging the gap between health and social care for rare diseases: key issues and innovative solutions. *Adv Exp Med Biol*. 2017;1031:605–627. https://doi.org/10.1007/978-3-319-67144-4_32. PMID: 29214594.
32 Uhlenbusch N, et al. Depression and anxiety in patients with different rare chronic diseases: a cross-sectional study. *PLoS One*. 2019;14(2):e0211343.
33 Currie G, Szabo J. 'It would be much easier if we were just quiet and disappeared': parents silenced in the experience of caring for children with rare diseases. *Health Expect*. 2019;22(6):1251–1259.
34 Gatta G, Trama A, Capocaccia R, RARECARENet Working Group. Epidemiology of rare cancers and inequalities in oncologic outcomes. *Eur J Surg Oncol*. 2019;45(1):3–11. https://doi.org/10.1016/j.ejso.2017.08.018. Epub 2017 Sep 19. PMID: 29032924.
35 Loeber JG, 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(1):15. https://doi.org/10.3390/ijns7010015. PMID: 33808002; PMCID: PMC8006225.

36 Unim B, Pitini E, Lagerberg T, et al. Current genetic service delivery models for the provision of genetic testing in Europe: a systematic review of the literature. *Front Genet*. 2019;10:552. https://doi.org/10.3389/fgene.2019.00552. PMID: 31275354; PMCID: PMC6593087.

37 OECD Health Statistics. Mueller, Bourke and Morgan. (2020[1]) "Assessing the comparability of Long-Term Care spending estimates under the Joint Health Accounts Questionnaire" https://doi.org/10.1787/health-data-en; 2020. https://www.oecd.org/health/healthsystems/LTC-Spending-Estimates-under-the-Joint-Health-Accounts-Questionnaire.pdf.

38 Baji P, Golicki D, Prevolnik-Rupel V, et al. The burden of informal caregiving in Hungary, Poland and Slovenia: results from national representative surveys. *Eur J Health Econ*. 2019;20(Suppl 1):5–16. https://doi.org/10.1007/s10198-019-01058-x. Epub 2019 May 14. PMID: 31089990; PMCID: PMC6544749.

39 Angelis A, Tordrup D, Kanavos P. Socio-economic burden of rare diseases: a systematic review of cost of illness evidence. *Health Policy*. 2015;119(7):964–979. https://doi.org/10.1016/j.healthpol.2014.12.016. Epub 2014 Dec 30. PMID: 25661982.

40 World Health Organization. *Primary healthcare on the road to universal health coverage. 2019 monitoring report: executive summary*. Geneva: World Health Organization; 2019 (WHO/HIS/HGF/19.1).

41 Héon-Klin V. European Reference networks for rare diseases: what is the conceptual framework? *Orphanet J Rare Dis*. 2017;12(1):137. https://doi.org/10.1186/s13023-017-0676-3. PMID: 28784158; PMCID: PMC5547471.

42 European Parliament and the Council of the European Union. Regulation (EC) No 141/2000 of the European parliament and of the council of 16 december 1999 on orphan medicinal products. Available at: https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32000R0141.

43 Huggett B. Drugmakers accused of exploiting orphan drug incentives, fueling price problem. *Nat Biotechnol*. 2017;35(4):301. https://doi.org/10.1038/nbt0417-301.

44 Tumiene B, Graessner H, Mathijssen IM, et al. European reference networks: challenges and opportunities. *J Community Genet*. 2021;12(2):217–229. https://doi.org/10.1007/s12687-021-00521-8. Epub 2021 Mar 17. PMID: 33733400; PMCID: PMC7968406.

45 Perrier L, Rascle P, Morelle M, et al. The cost-saving effect of centralized histological reviews with soft tissue and visceral sarcomas, GIST, and desmoid tumors: the experiences of the pathologists of the French Sarcoma Group. *PLoS One*. 2018;13(4):e0193330. https://doi.org/10.1371/journal.pone.0193330.

46 Derbel O, Heudel PE, Cropet C, et al. Survival impact of centralization and clinical guidelines for soft tissue sarcoma (A prospective and exhaustive population-based cohort). *PLoS One*. 2017;12(2):e0158406. https://doi.org/10.1371/journal.pone.0158406.

47 Casassus B. France promotes research into rare diseases with new plan. *Nat Med*. 2011;17(4):398–399. https://doi.org/10.1038/nm0411-398b. PMID: 21475215.

48 Taruscio D, Gentile AE, De Santis M, et al. EUROPLAN: a project to support the development of national plans on rare diseases in Europe. *Public Health Genom*. 2013;16(6):278–287. https://doi.org/10.1159/000355932. Epub 2014 Feb 3. PMID: 24503588.

49 Hedley V, Bottarelli V, Weinman A, Taruscio D. Shaping national plans and strategies for rare diseases in Europe: past, present, and future. *J Community Genet*. 2021;12(2):207–216. https://doi.org/10.1007/s12687-021-00525-4. Epub 2021 May 5. PMID: 33950416; PMCID: PMC8097119.

50 Stordeur S, Vrijens F, Leroy R. Reference centres for adults with rare and complex cancers - policy recommendations to improve the organisation of care in Belgium. *Rev Epidemiol Sante Publique*. 2016 Feb;64(1):1–6. https://doi.org/10.1016/j.respe.2015.11.006. Epub 2015 Dec 30. PMID: 26745998.

51 Directive 2011/24/EUof the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32011L0083.

52 *Report from the Commission to the European Parliament and the Council on the operation of Directive 2011/24/EU on the application of patients' rights in cross-border healthcare*. 2022 {SWD(2022) 200 final}.

53 Nabbe M, Brand H. The European health union: European union's concern about health for all. Concepts, definition, and scenarios. *Healthcare (Basel)*. 2021;9(12):1741. https://doi.org/10.3390/healthcare9121741. PMID: 34946467; PMCID: PMC8700883.

54 Mönig I, Steenvoorden D, de Graaf JP, et al. CPMS-improving patient care in Europe via virtual case discussions. *Endocrine*. 2021;71(3):549–554. https://doi.org/10.1007/s12020-021-02628-x. Epub 2021 Feb 2. PMID: 33528763; PMCID: PMC7851636.

55 European Court of Auditors. Special report: EU actions for cross-border healthcare: significant ambitions but improved management required (pursuant to Article 287(4), second subparagraph, TFEU), 2019. Available at: https://www.eca.europa.eu/Lists/ECADocuments/SR19_07/SR_HEALTH_CARE_EN.pdf.

56 Dos Santos Vieira B, Bernabé CH, Zhang S, et al. Towards FAIR-ification of sensitive and fragmented rare disease patient data: challenges and solutions in European reference network registries. *Orphanet J Rare Dis*. 2022;17(1):436. https://doi.org/10.1186/s13023-022-02558-5. PMID: 36517834; PMCID: PMC9749345.

57 Monaco L, Zanello G, Baynam G, et al. Research on rare diseases: ten years of progress and challenges at IRDiRC. *Nat Rev Drug Discov*. 2022;21(5):319–320. https://doi.org/10.1038/d41573-022-00019-z. PMID: 35079160; PMCID: PMC7613920.

58 Hedley V, Bolz-Johnson M, Hernando I, et al, Together4RD Steering Group. Together4RD position statement on collaboration between European reference networks and industry. *Orphanet J Rare Dis*. 2023;18(1):272. https://doi.org/10.1186/s13023-023-02853-9. PMID: 37670358; PMCID: PMC10478454.

59 Bolz-Johnson M, Kenny T, Le Cam Y, Hernando I. Our greatest untapped resource: our patients. *J Community Genet*. 2021;12(2):241–246. https://doi.org/10.1007/s12687-021-00524-5. Epub 2021 Apr 21. PMID: 33884523; PMCID: PMC8140952.

60 Andersen T, Le Cam Y, Weinman A. European reference networks for rare diseases: the vision of patients. *Blood Transf*. 2014;12(Suppl 3):s626–s627. https://doi.org/10.2450/2014.0039-14s. PMID: 24922305; PMCID: PMC4044799.

61 Mestre-Ferrandiz J, Palaska C, Kelly T, Hutchings A, Parnaby A. An analysis of orphan medicine expenditure in Europe: is it sustainable? *Orphanet J Rare Dis*. 2019;14(1):287. https://doi.org/10.1186/s13023-019-1246-7. Published 2019 Dec 11.

62 Zamora B, Maignen F, O'Neill P, Mestre-Ferrandiz J, Garau M. Comparing access to orphan medicinal products in Europe. *Orphanet J Rare Dis*. 2019;14(1):95. https://doi.org/10.1186/s13023-019-1078-5. Published 2019 May 3.

63 Subbiah V. The next generation of evidence-based medicine. *Nat Med*. 2023;29(1):49–58. https://doi.org/10.1038/s41591-022-02160-z. Epub 2023 Jan 16. PMID: 36646803.

64 Rosenberg N, Stolwijk NN, van den Berg S, et al. Development of medicines for rare diseases and inborn errors of metabolism: toward novel public-private partnerships. *J Inherit Metab Dis*. 2023;46(5):806–816. https://doi.org/10.1002/jimd.12605. Epub 2023 Apr 1. PMID: 36938792.

65 van den Berg S, de Visser S, Leufkens HGM, Hollak CEM. Drug repurposing for rare diseases: a role for academia. *Front Pharmacol*. 2021;12:746987. https://doi.org/10.3389/fphar.2021.746987. PMID: 34744726; PMCID: PMC8564285.

66 Plunkett-Rondeau J, Hyland K, Dasgupta S. Training future physicians in the era of genomic medicine: trends in undergraduate medical genetics education. *Genet Med*. 2015;17(11):927–934. https://doi.org/10.1038/gim.2014.208. Epub 2015 Feb 12. PMID: 25674779.