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ORIGINAL ARRTICLE

European Reference Networks: challenges and opportunities

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Abstract

European Reference Networks (ERNs) were founded on the principle that many rare disease (RD) issues are pan-European and any single Member State cannot solve them alone. In 2021, ERNs are already in the deployment stage; however, their day-to-day functioning and realization of their potential are still severely hampered by many challenges, including issues in governance and regulation, lack of legal status, insufficient and unsustainable funding, lack of ERN integration into national systems, endangered collaboration with UK RD experts due to Brexit, insufficient exploitation of ERN potential in RD research, underappreciation of highly qualified human resources, problems with the involvement of patient representatives, and still unclear place of ERNs in the overall European RD and digital ecosystem. Bold and innovative solutions that must be taken to solve these challenges inevitably involve pan-European collaboration across several sectors and among multistakeholder RD communities and in many cases crucially rely on the constructive dialogue and coherent, united decisions of national and European authorities that are based on common EU values. Importantly, unresolved challenges may have a strong impact on the further sustainability of ERNs and their ability to realize full potential in addressing huge unmet needs of RD patients and their families.

Background

European Reference Networks (ERNs) were founded on the principle that many rare disease (RD) issues are pan-European and any single Member State cannot solve them alone. Expertise and highly specialized services for RD diagnostics, treatment, and care are scattered across the European Union (EU). There is a critical lack of scientific knowledge and infrastructures for RD biomedical and clinical research. Only a small number of MS and regions have implemented RD-specific ORPHA coding into their healthcare systems; therefore, possibilities to trace RD patients in systems are limited, and principles of care organization are frequently unclear. High-quality healthcare provision is hampered by the severe lack of clinical practice standards and guidelines [Pavan et al. 2017]. Although physicians do not have sufficient information and knowledge on RD, especially those at primary care level [Vandeborne et al. 2019], very few universities have specific curricula for RD teaching. All of this leads to huge unmet needs of RD patients in all MS, but the problems in the Central-Eastern EU-13 countries that have comparably less resources available for healthcare are even greater.

ERNs have major potential to address many pan-European issues in RD, reduce inequities, and significantly increase accessibility to high-quality healthcare for any RD patient across the EU. Although they were established just 3 years ago and have just reached a deployment stage, the main "end-users" of ERN services—RD patients and families—already state that their healthcare experience in ERN centers is better [Rare Barometer 2021]. However, ERNs are still confronted with many challenges. Ironically, many of these challenges arise due to the pan-European nature of ERNs: in order to ensure effective functioning and sustainability of ERNs, there is a need to find means for a constructive dialogue and consensus between 27 MS and EEA countries and, in some MS, also between their regions. As the functions of ERNs are not limited to healthcare but also include integrated care, research, and education, intersectoral multidisciplinary collaboration is indispensable; however, there is a crucial lack of intersectoral governance. Finally, some ERN issues arise just because they are a disruptive innovation *per se*, pioneers without any precedent worldwide. "Disruptive innovation" is a concept that has been developed for analyzing ways to improve health outcomes and reduce costs [Hwang and Christensen 2008];

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however, implementation of these innovations into health systems requires appropriate organizational, legal, and financial frameworks. A key example is the fact that ERNs do not have a legal basis, because their structure does not fit into any of the established EU "legal frameworks." Some ERN services are completely innovative, e.g., virtual patient care through the Clinical Patient Management System (CPMS). CPMS may replace physical cross-border services and may enable high-quality, cost-effective, and patient-centered care provision; however, these services do not have a proper legal and financial basis as yet.

The readiness of ERNs themselves to adopt innovations was demonstrated during the COVID-19 pandemic: in the absence of any evidence-based resources, they managed to effectively develop guidance for patients and healthcare providers. Moreover, the ERN Information Technology and Communication (ITC) system was rapidly and effectively adapted to create a pan-European Clinical Management Support System (CMSS) for clinicians directly involved in the management of COVID-19 [European Commission website. European Reference Networks n.d.]. Unfortunately, still unresolved ERN issues indicate a lack of collaboration between MS and sectors and reluctance of authorities to take innovative, bold solutions that are required for the implementation of disruptive shared innovations. Importantly, unresolved challenges may have a strong impact on the sustainability of ERNs and their ability to realize full potential.

Conceptual framework

Legal basis of ERNs

EU actions in public health were formally enshrined in the article 168 of the Treaty on the Functioning of the European Union (TFEU): the EU shall complement national policies, encourage cooperation between MS, if necessary, and lend support to their action and may adopt incentives, measures, and recommendations designed to protect and improve human health and, in particular, to combat the major cross-border health scourges. In all its actions, the EU shall keep respect to the subsidiarity principle, i.e., responsibilities of the MS for the definition of their health policy and for the organization and delivery of health services and medical care [European Union 2012]. EU actions and responsibilities in RD and ERNs in so far as they concern cross-border healthcare were set out in the Directive 2011/24/EU on the application of patients' rights in cross-border healthcare [European Parliament and the Council of the European Union 2011]. Subsequent Commission Delegated Decision 2014/286/EU and Commission Implementing Decisions 2014/287/EU and 2019/1269 defined the general criteria and conditions for ERNs, including regulatory functions of the ERN Board of Member States (BoMS) [Commission Implementing Decision 2014; Commission Delegated Decision 2014]. As a result, the main responsibility for setting operational principles for ERNs remains with the BoMS, while the European Commission (EC) via DG SANTE takes coordination and implementation roles. The BoMS meets three times per year, on average. Additionally, various ERN governance and organizational issues are addressed through the BoMS working groups (WG). As these issues quite often require specific knowledge, analysis of the real situation, and "field work," joint BoMS and ERN coordinators' group (ERN CG) working groups (WGs) have been established since 2018, including WG on Ethical and Legal Issues, WG on ERN Integration into National Systems, WG on ERN Monitoring, WG on ERN Affiliated Partners, WG on Knowledge Generation, and WG on ERN Research [European Commission website. European Reference Networks n.d.].

Accountability of ERNs

ERNs and their members are accountable to both national and European institutions, and the main accountants are national authorities and the ERN BoMS, respectively. Designation, accreditation, and monitoring of RD Centers of Expertise (RD CoE) in every MS provide means to ensure high quality, centralization of resources and expertise, and cost-efficiency of RD highly specialized healthcare at a national level. CoE have to be endorsed to apply for the full membership in ERNs with the mandatory endorsement letter. Designation, accreditation, monitoring, and endorsement processes, however, differ significantly among the MS: some of them apply robust procedures, while in other, MS processes of quality assurance are less developed. All the applicants then go through a lengthy and robust assessment procedure that comprises activities of the respective ERN Boards, the Independent Assessment Body, and the ERN BoMS and includes both documentation analysis and on-site visits. Furthermore, compliance to the criteria is monitored through the continuous monitoring system. ERN full members (ERN FM) that no longer conform to the criteria may be subject to the non-compliance procedure and exclusion from the ERN under article 12 of the Commission Implementing Decision [Commission Implementing Decision 2014]. There are two sets of criteria for ERN Full Members: general criteria, defined in the Commission Delegated Decision and related documents [European Commission 2019], and specific or network criteria, defined by ERNs themselves [European Commission website. European Reference Networks n.d.].

MS that do not have CoE that conform to the criteria for ERN FM may designate ERN affiliated partners (ERN AP). ERN AP do not have an obligation to reach certain thresholds of compliance to the criteria, but they should execute activities related to the ERN with which they seek to affiliate. Although

ERN AP do not go through any assessment procedure at European level, they sign bilateral agreements by which they undertake to contribute to ERN activities.

Organizational structure

In preparation for ERN development, EU Commission Expert Group on Rare Diseases (EU CEGRD) issued a list of 21 thematic groupings of RD with a purpose to find a "home" for every RD and to define the scopes for every ERN [European Commission 2013]. Based on this list, a matchmaker tool was set up by a Joint Action Program RD-ACTION that highly facilitated interconnections of professionals and preparation of ERN applications [RD-ACTION n.d.]. Eventually, the first call for ERNs in 2016 resulted in the first set of 24 patient-centered ERNs that slightly deviated from this concept: two ERNs covered novel areas (rare epilepsies, child transplantations), rare gynecological and obstetric diseases were not covered by any ERN, and four ERNs covered the area of rare cancers and tumors [European Commission website. European Reference Networks n.d.]. Currently, these 24 ERNs include more than 950 ERN FM and more than 200 ERN AP, while the second call for ERN Full Membership may eventually result in up to 2000 ERN FM and ERN AP in total.

The general structure of ERN, defined by the Directive 2011/24/EU, may be described with a hub-and-spokes model, where ERN's coordinator is a hub and ERN's FM and ERN's AP comprise spokes. ERN's board consists of representatives of ERN FM and is the main body for decision-making in every ERN, while the main responsibilities for ERN administration, coordination, and legal representation lie with the ERN coordinator and its healthcare provider (HCP). In accordance with the principle of patient-centeredness, every ERN includes European Patient Advocacy Groups (ePAGs).

In real life, ERN structures are more complicated due to the vast nosological scopes and many functions of ERNs and include subnetworks for various RD groupings and work packages (WP) for transversal activities. In this way, ERN members may complement each other and share responsibilities. ERNs also differ greatly in size of patient populations and number of RD covered. The role of the ERN coordinator is very important: he or she must have skills in management, administration, leadership, collaboration, and networking; be able to bring together multistakeholder communities; represent them; and integrate into the overall RD ecosystem. In the process of ERN development, many of these leaders came from the scientific or professional organizations and/or previous European projects. Coordinators of all ERNs constitute ERN coordinators' group (ERN CG) that is the main body for representation of ERNs in the BoMS and any other institutions.

Many HCPs that host ERN FM are large and acknowledged academic hospitals, where highly specialized healthcare, research, and medical education are centralized (Table 1). Execution of ERN functions places an additional burden onto these hospitals and is usually not covered by specific state funding and support. To address these issues, the ERN hospital managers' group was established in 2017 with the aim to foster discussions and to identify solutions for these common challenges.

In bold are two HCPs from newcomer EU-13 countries

ERN functions

Every ERN is engaged in the triple obligation of highly specialized healthcare, research, and education that may eventually decrease multiple unmet needs of RD patients. Networking in ERNs has a high added value as it may provide access to knowledge, expertise, and highly specialized services across the EU to every RD patient in need and reduce inequities among MS. Furthermore, networking in ERNs may ensure economies of scale, scope, and speed for any task that is performed in collaboration. Eventually, the day-to-day functioning of ERNs include a vast range of activities that goes far beyond the usually ascribed virtual care provision and includes development and implementation of clinical standards and guidelines, development and provision of education and training curricula, creation and maintenance of registries, databases and biobanks, biomedical and clinical research, communication, dissemination, awareness raising activities, and many more. Administration and coordination of all these activities in ERNs result in a large workload, which falls mainly onto the shoulders of the ERN coordinators.

In 2020, ERNs are already in the deployment stage and more than halfway to the assessment of their overall performance in 2022. Unfortunately, functioning and realization of their potential are still limited by many challenges. Some of the key issues have been recently identified by the European Court of Auditors, including lack of a coherent strategy and solutions for ERN long-term sustainability and funding, integration of ERNs into national systems, their collaboration with industry, assessment and monitoring, data policies, ERN registries, and ERN governance [European Court of Auditors 2019]. Challenges of ERN integration into national systems and lack of support by the MS, along with the need for sustainable development and financing, were also recently raised in the Committee on the Environment, Public Health and Food Safety of European Parliament [European Parliament 2018]. However, ERN coordinators and members are in the best position not only to describe their key issues but also to offer some proposals and opportunities on how to address them.

Table 1 HCPs that host the highest numbers of ERN FM

1.	University Hospital Leuven	19	BE
2.	AO di Padova	18	IT
3.	Karolinska University Hospital	18	SE
4.	Erasmus MC: University Medical Center Rotterdam	18	NL
5.	Assistance Publique-Hôpitaux de Paris, Hôpital Necker-Enfants Malades	15	FR
6.	Pediatric hospital Bambino Gesù, Rome	15	IT
7.	Radboud University Medical Center Nijmegen	14	NL
8.	Great Ormond Street Hospital for Children NHS Foundation Trust	13	UK
9.	University Hospital Ghent	12	BE
10.	**Motol University Hospital**	**12**	**CZ**
11.	Academic Medical Center Amsterdam	12	NL
12.	University Medical Center Utrecht	12	NL
13.	Charité Universitätsmedizin Berlin	11	DE
14.	Universitätsklinikum Freiburg	10	DE
15.	Centro Hospitalar e Universitário de Coimbra, EPE	10	PT
16.	Hospital Universitari Vall d'Hebron	10	ES
17.	University Medical Center Groningen	10	NL
18.	University Hospitals Saint-Luc	9	BE
19.	Copenhagen University Hospital Rigshospitalet	9	DK
20.	Hospices Civils de Lyon	9	FR
21.	AOU Siena	9	IT
22.	Central Manchester University Hospitals NHS Foundation Trust	9	UK
23.	Assistance Publique-Hôpitaux de Paris, Hôpital Bicêtre	8	FR
24.	Klinikum der Universität München	8	DE
25.	Foundation IRCCS CA'Granda Ospedale Maggiore polyclinic - Milan	8	IT
26.	**Vilnius University Hospital Santaros Klinikos**	**8**	**LT**
27.	Leiden University Medical Center	8	NL
28.	Birmingham Children's Hospital NHS Foundation Trust	8	UK

ERN challenges and opportunities

Governance and regulation

ERN governance and regulation present several challenges, starting from the crucial question on who takes the main responsibility for the governance of ERNs: EU or MS? One of the key concepts in EU legal framework is a concept of subsidiarity, which is that tasks should be performed at the smallest unit possible. Usually, this is taken to mean that the EU should not do tasks that the MS could do better [Greer et al. 2019]. On the one hand, all ERN FM and ERN AP are integral parts of national systems, a national value that primarily gives benefits to its own country and citizens and operates within country's legal and organizational framework. On the other hand, no one single MS may have all the resources and expertise to solve RD issues alone; hence, MS must find solutions to these pan-European problems in a coherent, united, and effective pan-European way. In the governance of ERNs, interdependence of MS is particularly evident: it is imposible for ERNs to function based on 27 different solutions. Many ERN governance, sustainability, efficiency, and quality assurance issues have to be tackled at the EU level through a common pan-European strategy and clear principles of its implementation.

Another governance issue arises from the fact that ERN activities involve several sectors (healthcare, social care, research, and education) and require intersectoral collaboration. This intersectoral collaboration enables smooth innovation development and an implementation pipeline and successful integration of ERNs into the overall RD ecosystem. Unfortunately, unsolved question here would be, "May intersectoral collaboration be achieved without intersectoral governance?" Currently, the main institutions taking responsibility for ERN governance are DG SANTE and ERN BoMS that is composed of representatives of Ministries of Health of MS. These institutions are not always able to deal effectively with ERN issues that go out of the scopes of their mandates. Similarly, lack of intersectoral governance is also evident in the MS: out of the 25 national plans or strategies for rare diseases (NP/NS), 14 were signed by Ministers of Health only [EUROPLAN n.d.] (Table 2). Indeed, necessity to find

Table 2 Intersectorality of rare disease national plans or strategies in the EU

MS	Intersectorality of rare disease NP/NS	MS	Intersectorality of rare disease NP/NS
Austria	H + S + R	Ireland	H
Belgium	H + S	Italy	H
Bulgaria	H	Latvia	H
Croatia	H	Lithuania	H
Cyprus	H	Luxembourg	H
Czechia	H	Netherlands	H + R
Denmark	H	Norway	H
Estonia	H + S	Portugal	H
Finland	H + S	Romania	H
France	H + S + R + F	Slovakia	(Government) H + S + R + F
Germany	H + R	Slovenia	H
Greece	H + S	Spain	H + S
Hungary	(Ministry of Human Resources) H + S + R		

synergies at many levels (regional, national, European) and across sectors makes ERN governance a complex issue; however, many unsolved ERN problems stem out of lack of a proper and coherent governance model (e.g., ERNs are funded through multiple European and national sources and administration of budgets entails a huge administrative workload onto ERN Coordinators).

H health authority, *S* authority for social care, *R* authority for research, *F* finance authority

Finally, many ERN issues have to be solved on the ground, through self-government and self-management at the ERN board level. ERNs are diverse in terms of size and scopes and cover a diverse range of highly specialized areas; therefore, top-down, centralized, and "one-size-fits-all" solutions are quite often not feasible to implement.

Solutions and opportunities

It is evident that both the MS and the EU have a responsibility to govern and support the missions of the ERNs through the development of a coherent multilateral strategy and governance model. Given that pan-European issues cannot in principle be resolved in any single MS, it is essential to assign EU institutions not only with advisory and coordination functions but also direct regulation, enforcement, and implementation of decisions and accountability monitoring. ERN governing bodies must have sufficient powers to enforce implementation of decisions both in Europe and in each MS.

Intersectoral governance in the MS can be ensured through intersectorality of the RD NP/NS and the representation of ERNs in the national policy-making and policy-oversight bodies. Many NP/NS were developed in the pre-ERN era and need some updating and revision. As any strategical planning must be supported by the appropriate financial instruments and should take the good example of G20 response to COVID-19 crisis; involvement of financial authorities is imperative [https://www.gov.uk/government/news/g20-finance-and-health-ministers-statement-on-covid-19-response-17-september-2020]. Intersectoral governance and representation of ERNs should also be ensured in the EU institutions, at least through a constant liaison officer in every relevant DG of the EU.

Funding sustainability

Currently, there is no sustainable decision on who should fund ERNs and how. ERNs perform many interconnected functions, some of them are more national (e.g., direct healthcare services provided in the ERN FM and ERN AP), while others are more European (e.g., networking, CPMS, RD research, ERN registries).

EU funding is provided for the CPMS development and management, support for the development of CPGs, ERN registries, training programs, and some networking and administration activities. As EU funding is grant-based and involves several different sources and instruments, it entails a high administrative workload of application writing, management, and reporting [European Court of Auditors 2019] and does not ensure long-term sustainability for many long-term activities. Moreover, lack of legal status precludes application of sustainable funding instruments and participation in competitive funding calls, while possibilities to attract private funding resources are still unclear due to restrictions that were imposed by the ERN BoMS [European Commission website. European Reference Networks n.d.]. Finally, some ERN-provided services are not covered by any financial instruments. The prime example is the usage of CPMS: virtual clinical consultations for complex RD cases are given by

international groups of top-level experts and help to implement one of the most important missions of ERNs—cross-border transfer of knowledge and expertise without physical movement of a patient. Theoretically, CPMS could help countries save on cross-border healthcare and ensure accessibility of high-quality services across Europe. Unfortunately, as CPMS services are not covered and remain a "voluntary" and sometimes even "out of working hours" activity, it results in CPMS underusage and severely jeopardizes long-term sustainability of these valuable services.

MS have generously invested into the development of technologies and infrastructures and training of experts for highly specialized services, all of which eventually formed the basis for ERNs. In spite of this, national funding for ERN-related services and activities is still lacking in the majority of MS, including innovative service delivery models, networking and administrative activities, maintenance of infrastructures (e.g., collection of data for ERN registries), and national dissemination of excellence and expertise, among many others.

Solutions and opportunities

Long-term sustainability and execution of functions in ERNs are crucially dependent on the availability of appropriate national and European funding. The innovative nature of ERNs and their services require innovative funding models, and multisectoral ERN functions have to be covered through multisectoral budgeting. Beyond the inaugural stage, constant funding models should be applied to all long-term ERN activities. National funding should cover ERN-related services and activities that are provided by ERN FM and ERN AP of a respective MS. Some MS provide best practice examples of support (e.g., subsidy of 60K euros per year to each ERN coordinator in France, annual support of ERN FM and ERN AP in some MS, and surplus reimbursement rates for healthcare services provided to RD patients with ORPHA codes). Meanwhile, EU funding should be based on common EU values of solidarity, respect for human dignity and human rights and equality, and should ensure accessibility of ERNs to every citizen across EU. According to the recommendations of the European Court of Auditors, the EU budget should contain a specific budget line for ERNs and involve multiannual planning [European Court of Auditors 2019]. Some aspects of ERN governance and funding may include those applied to European Research Infrastructure Consortia (ERIC) [European Commission website. European Research Infrastructure Consortium (ERIC) (n.d.)]. Finally, collaboration of ERNs with the private sector is crucial, especially in the field of clinical research, and it is therefore essential to exploit the possibilities of private funding (such as pharmaceutical industry) while taking appropriate transparency and conflict of interest management measures. In conclusion, there is an urgent need for a constructive dialogue between the MS (including their relevant healthcare and research funding agencies) and EU institutions and bodies and development of a common long-term strategy for coherent, united, multisectoral national and European ERN funding.

ERN legal status

Currently, ERNs do not have legal status, and any legal or financial issues are managed through participating HCPs (most often those of ERN coordinators) based on their homeland legal frameworks. Lack of ERN legal status presents many challenges, including limited competitiveness in calls and less funding opportunities, complicated management of applications, grants and funds, variable and complicated legal frameworks that are dependent on many national legal frameworks (e.g., for informed consents and other ethicolegal and data protection issues), limited possibilities to have an impact on the implementation of ERN strategies and decisions (e.g., adoption of ERN CPGs in MS), diminished possibilities to have a strong representation and voice in external affairs (e.g., in EU institutions, calls and programs), and, finally, many day-to-day functioning issues related to self-management and self-governance of ERNs.

Solutions and opportunities

Certain aspects of the ERIC model could be applied to the ERNs; however, ERN functions go far beyond provision of resources and services for research. Hence, flexibility and openness to innovation are highly important, as there is no precedent for ERNs in the EU, and all the MS have to find a common solution for their legal status.

ERN integration into national systems

The importance of proper ERN integration into national systems was acknowledged by many external evaluators [European Court of Auditors 2019; European Commission 2018; European Parliament 2018] and ERN BoMS [European Commission website. European Reference Networks n.d.] and has been emphasized many times by the ERN coordinators and members themselves. Indeed, as each ERN FM and ERN AP functions in its own national system, their performance, and eventually the overall performance of ERNs depends in many ways on the national systems. On the other hand, the MS may reap the benefits of ERNs only when they are properly integrated into national systems. It is not just national funding that is important. RD patients of each MS enter ERNs only when care pathways and referral systems are in place and functioning. Treatment outcomes and even overall survival rates are crucially dependent on the application of evidence-based high-quality clinical standards along the whole care pathway; hence, there is a need for proper

navigation of patients' data and funds and means for communication and collaboration across the system [Kalaiselvan et al. 2019; Derbel et al. 2017; Perrier et al. 2018]. Importantly, proper ERN integration into national systems may also help to tackle wasteful spending on RD healthcare (e.g., due to duplicated or redundant services, lack of centralization of resources, and low quality services) [Socha et al. 2017].

Solutions and opportunities

A general framework for ERN integration into national systems along with a non-exhaustive list of proposed measures was recently issued by the ERN BoMS [European Commission website. European Reference Networks n.d.], and many MS have already taken some decisive steps. As national systems across the EU are highly diverse, there are no one-size-fits-all solutions: every MS has to take its own decisions. National workshops involving national authorities, ERN coordinators and/or members, representatives of BoMS, patients' organizations, funding organizations, and other stakeholders are already ongoing in some MS. However, there is a need to set up some general principles, e.g., on the establishment of care pathways and organization of RD healthcare and on the identification of RD-specific indicators and measures for situation analysis and monitoring.

As many NP/NS for rare diseases were developed in the pre-ERN era, they need some updating and revision. Similarly, cancer NPs should also include measures for proper integration of ERNs for rare cancers and tumors [Joint Action Rare Cancers 2030]. National networks were established in some larger MS and provide basis for RD care pathways [Plan National Maladies Rares 2018-2022]. Interregional collaboration reduces regional inequities and provides means for care pathways and referrals to ERNs in regionalized healthcare systems [Nuti et al. 2017; Harrison et al. 2015]. Centralization of services through designation and accreditation of RD CoE and careful endorsement of applicants for ERN FM ensure saving of scarce resources and provision of high-quality services [Pasquali et al. 2019; Peycelon et al. 2017; Pakarinen et al. 2017]. Indeed, the rich diversity of systems and solutions to common challenges across EU means that sharing of experiences and best practice examples between MS may be highly beneficial.

Sustainability in numbers

The first ERN call came as a surprise to some: instead of the expected 10 to 12 ERNs with 10 to 12 members in each, more than 950 centers eventually became ERN FM of the 24 ERNs. Following the call for affiliated partners, the total number of ERN FM and ERN AP exceeds 1200, and after the second call for full membership, total number may reach up to 1800 ERN FM and ERN AP in 2021.

Despite such large numbers, ERN scopes are still not complete: many ERNs have incomplete geographical and nosological coverage. Some MS do not have ERN FM or ERN AP in ANY ERN, while others are directly involved in all 24, and each ERN has a geographic coverage of 17 to 27 MS. Some ERNs do not fully cover the nosological range (ORPHA codes) of their thematic RD groupings, and entirely new ERNs may be established in the future, e.g., ERN for rare infections or ERN for rare gynecological and obstetric diseases (outside cancers). The current extent of ERNs is also not surprising given recent data on RD prevalence: at any given time, patients with RD comprise 3.5 to 5.9% of a population, excluding rare cancers, intoxications, and infectious diseases [Nguengang Wakap et al. 2020]. Therefore, more than 1 million ERN patients per year reflect only a small fraction of all RD patients in the EU (i.e., around 30 million people). Besides, there are up to 8000 RD in total; therefore, many ERNs have vast nosological scopes and include many subnetworks, where any given ERN FM or ERN AP covers a limited number of RD in the relevant thematic RD grouping.

Of course, large numbers of ERN FM and ERN AP impose serious issues of manageability, sustainability, governance, and funding, while their highly unequal distribution across Europe (and across regions in some MS) results in remaining inequities and limits ERN accessibility. The situation is partly due to the regulations defined in the Directive 2011/24/EU on the application of patients' rights in cross-border healthcare: on the one hand, ERNs "shall at all times be open to new HCPs which may wish to join them, provided that such HCPs fulfill all the required conditions and criteria"; hence, there are no means to deny full membership to the CoE that conform to the criteria and have endorsement letters from the respective national authorities, even though there are already many other ERN FM from the same MS. On the other hand, as "the networks shall be based on voluntary participation by its members," there are no means to enforce participation of MS with small numbers of ERN FM and ERN AP [European Parliament and the Council of the European Union 2011].

ERN accessibility across Europe is ensured through affiliated partnership in countries where capacities in RD care are limited. Exceptional ERN inclusivity compared to, e.g., programs for EU research funding [Harrap and Doussineau 2017; Kaló et al. 2019] is demonstrated by the number of ERN FM and ERN AP in the EU-13 countries, where 20% of the EU inhabitants live: after the first call for ERN FM, the percentage of ERN FM in EU-13 MS was 11.3%, while after the call for ERN AP, 20% of all ERN FM and ERN AP were in the EU-13 MS (Table 3). Despite this, huge inequities among all MS remain: in 2020, the number of ERN centers per million of inhabitants ranges from < 1 ERN center/mln. inh. (GR, RO, PL, IE, BG) to > 10 ERN centers/mln. inh. (LT, CY, LV, EE)

Table 3 Numbers of ERN FM and ERN AP in the MS

	Population	Full members (ERN FM)	ERN FM/ mln. inhabitants	Associated partners (ERN AP)	Total (ERN FM and ERN AP)	Total/mln. inhabitants
Greece	10.8	0	0	0	0	0
Romania	20	7	0.35	2	9	0.45
Poland	38	21	0.55	1	22	0.58
Ireland	4.6	3	0.65	0	3	0.65
Bulgaria	7.2	7	0.97	1	8	1.11
Germany	81	121	1.49	0	121	1.49
Spain	46	42	0.91	34	76	1.65
UK	65	112	1.72	0	112	1.72
Slovakia	5.4	0	0	10	10	1.85
France	66	124	1.88	0	124	1.88
Norway	5.2	4	0.77	6	10	1.92
Malta	0.5	0	0	1	1	2
Hungary	10	14	1.4	7	21	2.1
Czechia	10.5	29	2.76	0	29	2.76
Portugal	10.3	30	2.91	0	30	2.91
Sweden	10	30	3	0	30	3
Italy	61	188	3.08	0	188	3.08
Finland	5.4	14	2.59	4	18	3.33
Luxembourg	0.6	1	1.67	1	2	3.33
Netherlands	17.5	90	5.29	0	90	5.29
Austria	8.6	2	0.23	48	50	5.81
Belgium	11.3	67	5.92	0	67	5.93
Croatia	4.2	2	0.47	24	26	6.19
Denmark	5.7	17	2.98	28	45	7.89
Slovenia	2	9	4.5	8	17	8.5
Lithuania	2.8	12	4.29	16	28	10
Cyprus	0.9	2	2.22	8	10	11.11
Latvia	2	2	1	32	34	17
Estonia	1.3	3	2.31	20	23	17.69
		Sum: 953	Average: 1.92	Sum: 251	Sum: 1204	Average: 4.53

and differs 10 and more times. Similar inequities are also observed when comparing some MS regions, e.g., southern and northern regions of Italy. It should be noted that, in general, a higher ERN centers/mln. inhabitants indicator is typical of smaller countries.

From: European Commission website. European Reference Networks n.d.. Available at: https://ec.europa.eu/health/ern_en

Solutions and opportunities

Given the prevalence of RD collectively (which is, actually, higher than the prevalence of type I diabetes or epilepsy), it is great that we have so many RD CoEs in Europe. However, not every RD CoE should be ERN FM or ERN AP; otherwise, ERNs will be unmanageable and unsustainable. Unfortunately, the simple hub-and-spoke model defined in the Directive probably does not correspond to the current real situation. Although political decisions may sometimes induce tensions in the MS, ERNs must become networks of networks: in each MS, and especially in larger ones, all RD CoE should be joined into the national networks, and the representatives of these networks should represent their country in each ERN. A similar management model is already in place in ERN GENTURIS. Care pathways and systems of referral to ERNs ensure proper connections across national networks and spread of ERN-developed knowledge and expertise into the systems.

Moreover, national authorities have to take seriously their responsibilities to ensure high quality in RD CoE. In some of MS, there is a high need for robust procedures for the designation, accreditation, and quality assurance of RD CoE and endorsement for ERN full membership. In time, the number of

ERN FM may decrease due to the continuous evaluation: a comprehensive assessment of ERN activities is foreseen in 2022, while non-compliance procedures and exclusion from ERNs may already be applied to those centers that no longer meet ERN FM criteria that are monitored continuously [European Commission website. European Reference Networks n.d.]. In this way, ERNs may eventually eliminate those HCPs that have entered ERNs with the aim to improve their reputation, but not to create a common public good.

On the other hand, while taking measures to limit numbers of ERN centers, one of the main purposes of ERNs must never be forgotten: i.e., to ensure ERN accessibility to every European RD patient in need. Therefore, the doors to ERNs must be secured for citizens of each MS and region. Fostering participation in ERNs is especially important in some currently under-represented countries.

Uncertainties due to Brexit

Expertise of RD experts from UK is highly valuable; in 2017, UK hosted six ERN coordinators and 112 ERN FM, and many British patient representatives joined the ERN ePAGs. In April of 2019, ERN coordinators from UK had to pass ERN coordination to HCPs from other EU countries; meanwhile, perspectives of further collaboration of UK and ERNs post 2020 (when UK HCPs cease to be official members) are still unclear.

Solutions and opportunities

It is highly important to ensure as tight a collaboration as possible between UK and ERNs, as loss of it may negatively affect both sides significantly.

Research-based care and exploitation of ERN potential in research

In view of a very scarce knowledge on the majority of RD, patients and their families frequently have to deal with a so-called scientific uncertainty: even the most experienced professionals may be unable to provide sound data and guidance on disease diagnostics, management, prevention, and prognosis. In these situations, it is very important to recognize this uncertainty, share responsibilities, and empower patients and their families. Besides, almost every patient diagnosed with a RD becomes a precious source for further RD research, including collection of clinical data for natural history studies, biospecimens for the development of diagnostics and biomarkers, and creation of disease models. Due to the scarcity of both RD patients and experts, strong collaboration between MS and globally in RD research becomes a *sine qua non* condition; this collaboration provides economies of scale, scope, and speed. Actually, only a few of the larger MS have national or regional research programs dedicated specifically to RD research [RD-ACTION 2018]. Direct and smooth interface between highly specialized healthcare and research also ensures efficient and rapid knowledge generation, innovation development, and implementation into clinical practice. The importance of moving towards research-based care was exemplified by several major initiatives, like 100,000 Genomes Project in UK and Care4Rare in Canada [Turro et al. 2020; Frésard et al. 2019]. In 100,000 Genomes Project, a nationwide initiative ensured alignment of genomic sequence data with medical records to create a groundbreaking research resource; thousands of patients received precise genetic diagnosis, actionable findings were found for one in 4 to one in 5 RD patients, and in 50% of cancer cases, potential for a therapy or a clinical trial was identified. Moreover, innovations of genomic medicine were translated into clinical practice [Turnbull et al. 2018].

With more than 1200 ERN centers, ERNs comprise the largest platform for clinical research and translation worldwide. Unfortunately, realization of ERNs' research potential is hampered by several challenges. ERNs are an important part of the main and the most comprehensive RD research program to date—European research program on RD (EJP RD) [European Joint Programme for Rare Diseases, n.d., website]. However, although ERNs are active participants in its joint transnational calls, education and training activities, clinical research, and some other activities, the funding provided by the EJP RD is insufficient to exploit the full research potential of ERNs. Problems also arise due to the lack of ERN legal status: research calls and programs involve individual ERN centers rather than the entire ERN, and it significantly reduces the competitiveness and potential of ERNs. Moreover, collaboration with industries and participation in research that is entirely or partially funded by industries may be restricted due to the conflict of interest regulations imposed by the BoMS [European Commission website. European Reference Networks n.d.]. In RD biomedical and clinical research, where only a critical number of patients may enable solving unanswered questions and identification of novel treatments, all these challenges severely limit research potential of ERNs. Finally, in some MS, ethicolegal regulations impose a clear distinction between the two contexts of healthcare and research and induce large workloads and complex and lengthy procedures to arrange, manage, and implement research [Bertier et al. 2018].

Solutions and opportunities

The organization and funding of research and research-based care in ERNs are highly dependent on the decisions of national and European authorities. Decisions should be taken on the development of a coherent ERN research strategy, funding sources and instruments, alignment of national and European RD research programs, fostering of EU-wide and global cooperation in RD research, and collaboration of ERNs

with private sector. Management of ethicolegal issues could be facilitated by the establishment of ERN legal status and a "centralized" approach.

Human resources in ERNs: expertise cannot be taken for granted

To become an expert in RD, every ERN professional has to go a long way: expertise and skills required for highly specialized RD care have to be superimposed onto the wealth of general knowledge and skills that is acquired with a conventional medical education and involves 10 to 13 years in many countries. Integrated multidisciplinary RD care demands "soft skills" that are required for teamwork, networking, and care coordination. Besides, each ERN is obliged to engage with the triple activities of highly specialized healthcare, research, and education. Hence, there is a need for specific skills and know-how to carry out RD research (e.g., know-how on how to set-up and maintain a registry; collect and analyze high-quality, robust data; conduct small population clinical trials; and ensure management of data and legal and bioethical issues) and abilities to collaborate effectively with professionals from other fields (e.g., basic research, statistics, and biology). In current practice, changed by omics technologies, global networks for undiagnosed diseases, gene therapies, and many other emerging innovations, research-oriented medical education and development of capabilities to work in research teams are of ever increasing importance. ERN professionals are actively engaged into specialized medical education and training and need pedagogical skills and capabilities. In particular, many unusual tasks that require unconventional abilities and skills lie on the shoulders of ERN coordinators. These professionals must not only demonstrate leadership in a particular professional field but also be able to bring together colleagues with very different national backgrounds, understand various processes required to perform multiple ERN functions, and integrate ERNs into a common RD ecosystem.

European medical schools are often criticized for outdated and rigid teaching methods that do not equip students with the capacity to innovate and adapt to constantly emerging new challenges [OECD 2020]. Moreover, many current healthcare practitioners received their medical education at a time when RD concepts were not even developed. Indeed, RD experts need to be open-minded and ready to be proactive by nature and take a lifelong learning approach.

Acquisition and maintenance of RD and ERN-related abilities and skills require enormous effort, time, and appropriate conditions. Unfortunately, these abilities are not sufficiently valued and promoted in our national systems, and professional salaries are often calculated on the basis of the number of cases per unit time. For these reasons, there is a significant danger of loss of expertise as older colleagues retire; young people are not always as willing to embark upon a long journey which requires huge but underappreciated efforts.

Solutions and opportunities

It is important to acknowledge that RD and ERN activities require exceptional knowledge and skills, to provide opportunities to acquire them, to ensure adequate remuneration of highly qualified staff, and to facilitate career development of young professionals. ERNs themselves have vast resources that may be exploited through training, internship and exchange programs, support for networking, and peer learning.

Patient-centeredness in ERNs

Increasing patient-centeredness is a general trend in healthcare, but in RD area, it is of special importance. As local professionals frequently have limited knowledge of RD, patient empowerment and their capabilities to apply self-management are highly important. The voice of RD patients and their families is very important for raising awareness among lay public and authorities, and representatives of RD patient organizations are usually invited to national and European RD policy bodies. Due to the lack of knowledge on how to organize healthcare for RD patients, patient-reported experience measures may be highly valuable, while patient-reported outcome measures are increasingly used in clinical research, as there is a lack of objective outcome indicators for thousands of RD [Slade et al. 2018]. Finally, international patient organizations are very important, as RD patients are scarce and scattered across Europe.

In the ERNs, ePAGs participate in a wide range of ERN activities, including ERN boards and working groups. However, it is still very difficult to achieve their active participation: there is a general tendency for patients to share their experience in social media groups, but not to organize formal organizations, and many patients feel they lack the capacity to join and are insufficiently supported. Indeed, there are no specific allocations of EU funds for facilitation of patients' involvement, and national support to patient organizations is insufficient, especially in the MS with limited resources.

Solutions and opportunities

Collaboration between ERNs and national and international patient organizations, such as EURORDIS, should be strengthened, especially in the education and capacity building of patient representatives for their active engagement into ERN activities. Besides, it is highly important to provide both national and European funding for active patient engagement.

Place of ERNs in the EU RD ecosystem

The establishment of ERNs profoundly changed the entire RD ecosystem that was suddenly expanded by a huge number of HCPs and professionals from various RD fields. Although many of these professionals worked in the narrow field of RD for decades, usually they were more active in specialized medical fields (e.g., professional organizations) than in RD policy-making or other general RD activities. The intensive process of ERN community development and its integration into the common RD ecosystem took place in the first years of ERN development. Activities of a joint program RD-ACTION, including trainings and forums for joint discussions, played an important role. ERN CG, a group that is particularly active in the management of general ERN issues and representation of ERNs, was established. The involvement of ERN CG members into the joint BoMS/ERN CG working groups and into the EJP RD operating group helps to effectively address some important ERN issues. Interconnections with other stakeholders of the RD ecosystem are also important; e.g., appointment of a representative of the European Medicines Agency facilitates management of ERN clinical research, ERN ePAGs and collaboration with EURORDIS facilitate patient-centeredness, cooperation with Orphanet results in improvement of ORPHA coding system, and cooperation with the European Rare Disease Registry Infrastructure (ERDRI) and EJP RD helps in the development and FAIRification of ERN registries. Although RD are an important part of personalized medicine, the role of ERNs in some relevant EU personalized medicine initiatives like "Towards 1 million genomes" is currently unclear. Similarly, many issues of ERN data management, including prospects for the use of real-world data (RWD) and applications of artificial intelligence, and their place in the European single digital market, also remain unclear.

Solutions and opportunities

In order to exploit potential of ERNs and to embed them effectively into the national and European RD ecosystems, it is very important to ensure proper ERN representation and collaboration with many current and future initiatives.

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