Rare2030

Foresight in Rare Disease Policy

A knowledge-base summary concerning

ACCESS TO HEALTHCARE FOR RARE DISEASES

https://www.rare2030.eu/our-work

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1. INTRODUCTION TO THE TOPIC

This document will highlight a number of issues with a broad relevance to accessing healthcare for rare diseases, most notably: the creation and functioning of **Centres of Expertise** for rare diseases; the emergence and evolution of **European Reference Networks** (ERNs); the development and use of **clinical practice guidelines/clinical decision support tools** to reduce inequalities in care; **eHealth**; and **training and education**.

The lack of patients living with any single rare disease has traditionally been accompanied by a corresponding lack of experts able to properly diagnose, treat, and care for them. This inevitably created a 'geographical lottery', in which patients 'fortunate' enough to live reasonably close to true experts in their conditions might hope to benefit from the fruits of their knowledge and experience (accrued through a concentration of patient cases across the years). However, the majority of patients would be limited to the best their local hospital or tertiary care centre could offer, even though the expertise in their particular condition may be minimal. Numerous approaches and tools have been identified at European level, to try to eradicate such inequalities (which can often exist *within* countries, as well as between countries).

At the heart of a European system of rare disease healthcare is the concept of a Centre of Expertise. Indeed, in its simplest form perhaps, the vision of an ERN was to connect nationally-embedded centres of expertise for rare diseases and specialised healthcare, via virtual, transnational networks. Unsurprisingly, these concepts occupy an important position in the foundational policy documents which have driven so much of European rare disease activity in the past decade:

The Commission Communication on Rare Diseases: Europe's challenges (2008) [679 final] highlighted the need for "**Improving universal access to high-quality healthcare for rare diseases, in particular through development of national/regional centres of expertise and establishing EU reference networks**" (5.1)

The two topics were grouped together in SECTION 4 of the Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02: specifically, Member States were asked to

- "Identify appropriate centres of expertise (CEs) throughout their national territory by the end of 2013, and consider supporting their creation.
- Foster the participation of CEs in ERNs respecting the national competences and rules with regard to their authorisation or recognition.
- Organise healthcare pathways for patients suffering from rare diseases through the establishment of cooperation with relevant experts and exchange of professionals and expertise within the country or from abroad when necessary.
- Support the use of information and communication technologies such as telemedicine where it is necessary to ensure distant access to the specific healthcare needed.
- Include, in their plans or strategies, the necessary conditions for the diffusion and mobility of expertise and knowledge in order to facilitate the treatment of patients in their proximity.
- Encourage CEs to be based on a multidisciplinary approach to care when addressing rare diseases"

2. CENTRES OF EXPERTISE FOR RARE DISEASES

The concept of 'Centres of Expertise' is of major relevance to the rare disease field, as it encompasses a goal of mapping and understanding the existing rare disease expertise available in countries, but also exacts particular standards and quality criteria necessary in highly specialised care. Based upon the work of groups including the High Level Group on Health Services and Medical Care and the EC Rare Disease TaskForce, the EUCERD (EU Committee of Experts on Rare Diseases) elaborated a set of recommendations which were adopted on 24 October 2011: the EUCERD Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases in Member States.

This consensus-building on what constituted a Centre of Expertise (CE) was deemed especially important in the lead-up to the creation of ERNs: the selection and endorsement of national centres to participate in ERNs would presumably be facilitated for countries which had agreed formal processes for designating expertise in rare diseases. The drive for countries to endorse centres to formally join ERNs has, in some ways, reignited the topic of Centre of Expertise designation. Each country was responsible for defining its own procedure by which to endorse a Centre (HCP in the ERN vernacular) to participate, and naturally these criteria varied. For some countries, the logical approach – given the particular relevance of ERNs to rare disease– was to only endorse national centres which had formally been designated as a centre of expertise (or similar) for rare diseases. Other countries, including those which did not have a formal process in place for designating CEs for rare diseases, chose other ways to endorse centres to apply for ERN membership.

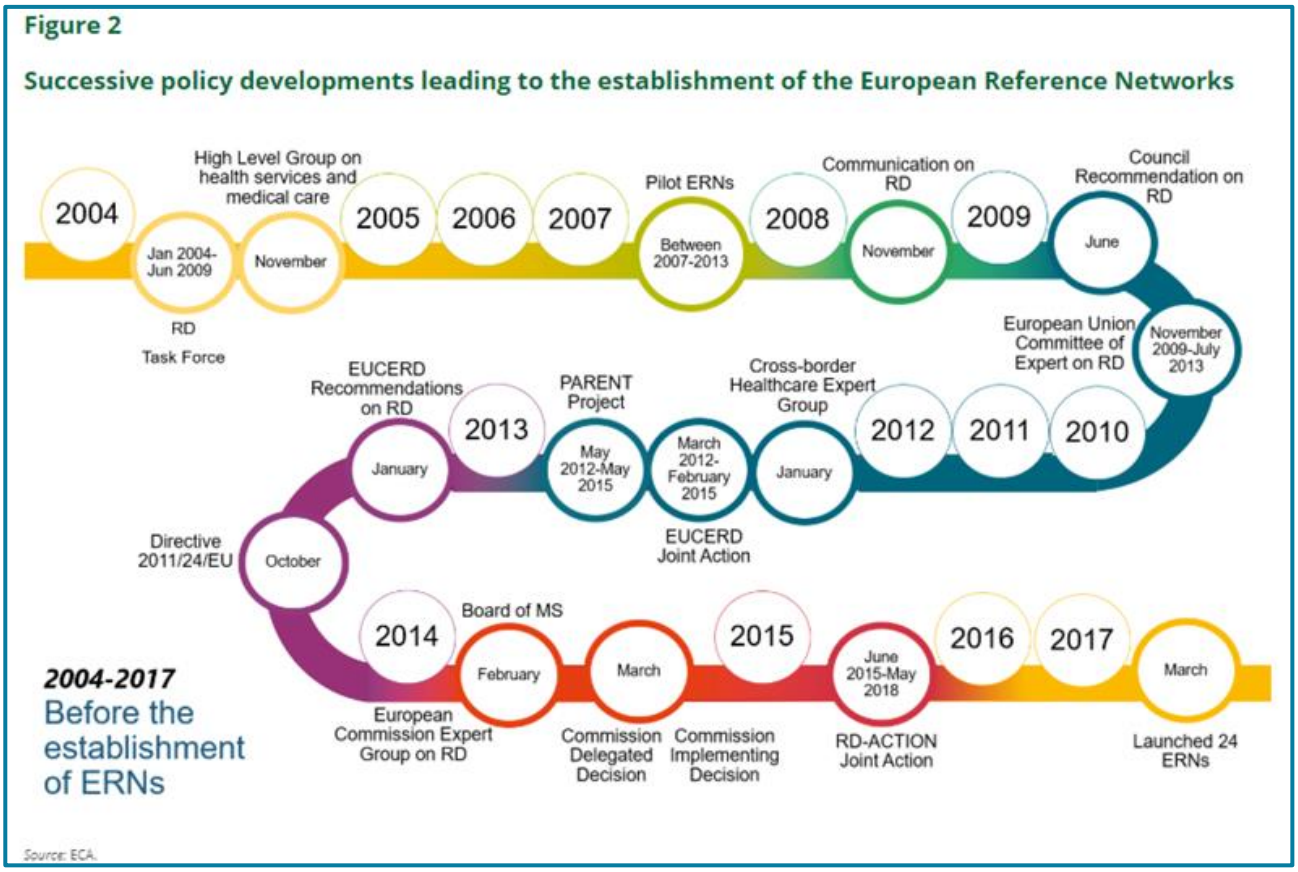
The result is a patchwork of over 900 HCPs (some hospital trusts, some individual centres, some specialised units within a wider hospital) organised into 24 ERNs: all should have been designated and evaluated at national level to comply with the core criteria for ERN HCPs as per the Delegated and Implementing Acts. But in some cases, these centres will have gone through detailed national designated processes *predating* the HCP designation in 2016.

3. THE ERA OF EUROPEAN REFERENCE NETWORKS (ERNS)

3.1. Policy and Legislative Origins of ERNs

- In 2011, the concept of an ERN formed the focus of Article 12 of the Directive on the Application of Patients' Rights in Cross-Border Healthcare (often termed the 'Cross-Border Healthcare Directive')
- The EUCERD adopted Recommendations on Rare Disease European Reference Networks on 31st January 2013
- These Recommendations were supplemented with an Addendum in 2015 (proposing a model to thematically group RD into a manageable number of networks, and outlining what meaningful patient involvement in ERNs might look like)
- The European Commission published the Delegated Decision (2014/287/EU) and Implementing Decision (2014/286/EU) on 10th March 2014. The Delegated and Implementing Decisions stipulated transversal criteria for networks to fulfil in order to qualify as ERNs and for healthcare providers wishing to join an ERN

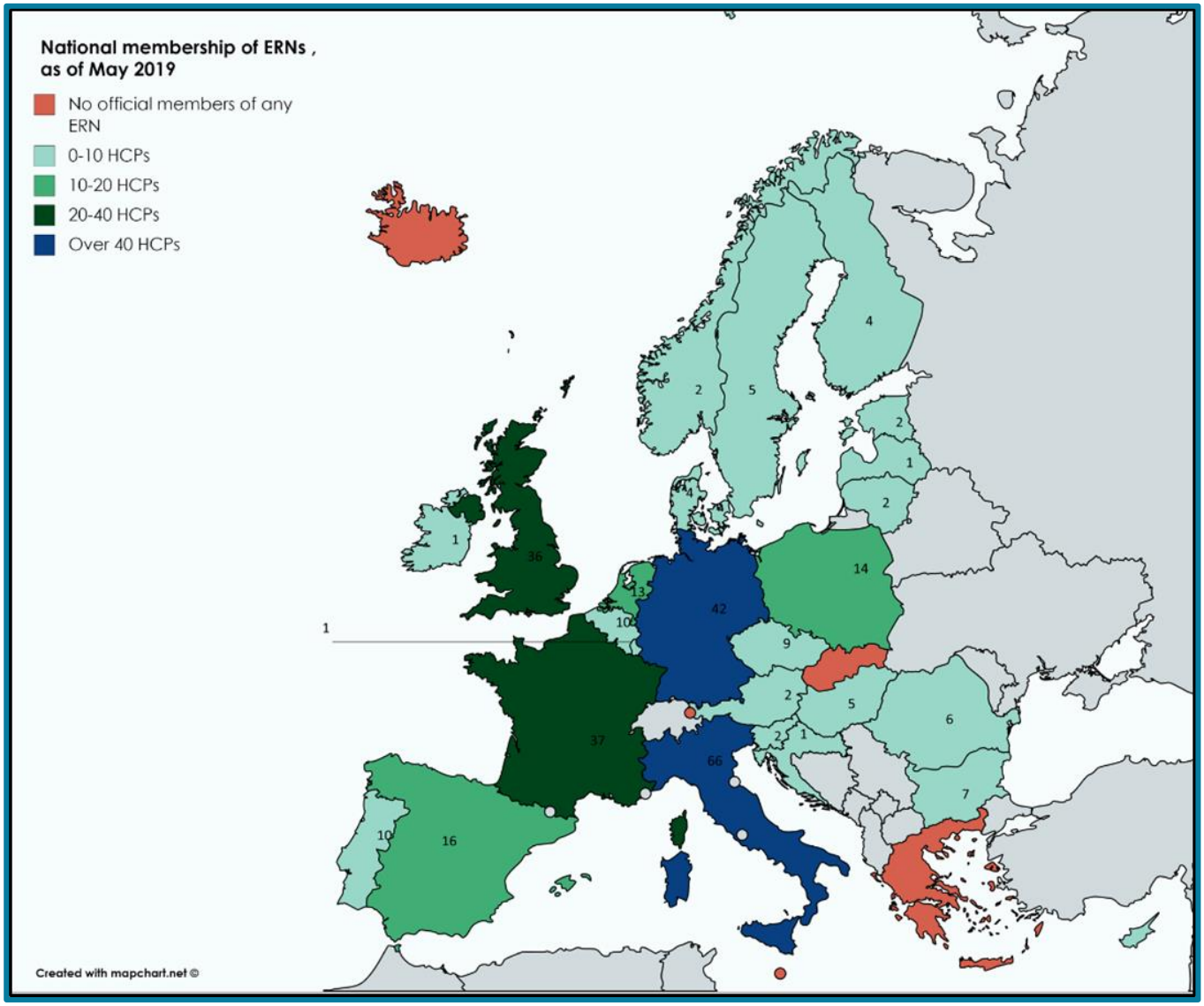
24 ERNs were officially approved as of January 2017, the result of over a decade of advocacy and planning at European and national levels. The road to ERNs is explained in more detail, here (pages 48 onwards).



(Image from the European Court of Auditors Report on the Implementation of Directive 2011/24/EU - http://publications.europa.eu/webpub/eca/special-reports/cross-border-health-care-7-2019/en/)

Support for the conceptualisation and implementation of ERNs was a cornerstone of two European Joint Actions for Rare Diseases – in *RD-ACTION particularly*, emphasis was placed on enabling the Networks to come together and address challenges around their common responsibilities, by sharing good practices and avoiding the reinvention of wheels.

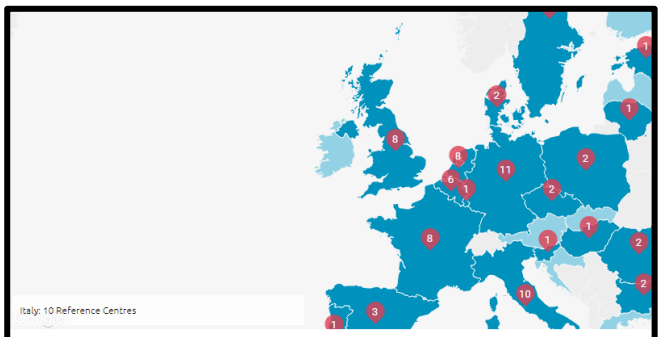
ERNs offer many advantages, in terms of bridging the care and research divide, which will -it is hoped- help to erode the inequalities observed to-date. A summary of each ERN is available here: https://ec.europa.eu/health/ern/networks_en. Together, the 24 ERNs unite over 900 specialist units in over 300 hospitals across 26 countries (25 EU MS –all except Greece, Malta, and the Slovak Republic- plus Norway, as an EEA nation). This map illustrates the current membership, based upon the official figures appearing on the European Commission websites, here.



3.2. How ERNs are elucidating the status quo for rare diseases and highlighting specialised care in Europe

The disease-coverage of ERNs is expected to increase via a step-wise approach, to ultimately offer the best possible advice and expertise on *all* conditions under each broad thematic umbrella heading (e.g. rare heart disease). Certain conditions could justifiably fall under the 'Grouping' of more than one ERN, thus a comprehensive mapping of which Network is focusing on which conditions is important.

It is important to emphasise that ERNs do not exist solely for rare diseases. They also unite providers of highly specialised healthcare including centres providing specialised procedures and surgeries which, whilst not necessarily associated with a single pathology, require a concentration of expertise and patients and will never be suitable for routine deployment in a large number of centres. Examples include specialised urogenital surgery (as advanced in the eUROGEN Network, for instance; paediatric transplantation (as is the focus of the EuroTransplantChild Network); and techniques such as proton beam therapy.



Distribution of Reference Centres by country

Participating Reference Centres (RCs)

Showing 71 RCs

RC Name	Country	City	Member of MTGs
Cliniques universitaires de Bruxelles – Hôpital Erasme	Belgium	Brussel	1 2 5 6 7 8
Cliniques universitaires Saint-Luc	Belgium	Brussel	1 3 4 5 6 7 8
UZ Brussels	Belgium	Brussel	6 7
Ghent University Hospital	Belgium	Ghent	7
UZ Leuven	Belgium	Leuven	3
Centre Hospitalier Universitaire de Liège	Belgium	Liege	4 6
USHATE "ACAD IVAN Penchev"	Bulgaria	Sofia	4 6
MHAT "Sveta Marina"	Bulgaria	Varna	3 7

Many ERNs have carefully mapped the specific expertise of HCPs within their networks, making such information publically available via their own websites (see right, an example from the ENDO-ERN website, illustrating the sub-domains of 'rare endocrine diseases' in which each member centre (here labelled as RC, Reference Centres) possesses the requisite expertise (https://endo-ern.eu/about/reference-centres/).

A related -and also very powerful- activity is the development of consensus **disease or disease-area specific criteria** for the conditions under the heading of each ERN. Such 'vertical' criteria in fact constitute a robust pan-European attempt to define what truly constitutes expertise in, for instance, inherited metabolic diseases or rare eye disease etc. These criteria specify patient numbers, necessary equipment/procedural skills, and the medical, multidisciplinary and paramedical expertise that should somehow be accessible by any HCP claiming expertise in each domain. As such, they hold major potential for countries perhaps seeking to determine disease-related criteria to supplement the cross-cutting EUCERD criteria of 2011 on Centres of Expertise for RD. These 'ERN network specific criteria' are available to download here.

3.3. ERN Operations in 2019

ERNs are now functioning individually, most notably perhaps in building up their numbers of cross-border referrals (see below). However, they are also initiating inter-ERN activity (around registration of patients, for instance) and indeed are cooperating at a strategic level via Working Groups overseen by the ERN Coordinators' Group.

'DATA TRAVELLING, RATHER THAN PATIENTS'

A key pillar upon which the ERN concept is based is the mantra that wherever possible, data should travel, rather than patients themselves. In reality, this meant the creation of a robust, secure platform to exchange data between HCPs based in different EU MS/EEA countries. The European Commission supported the provision of a suitable platform, which is today known as the CPMS (Clinical Patient Management System). **The CPMS itself offers significant potential to reduce inequalities in accessing healthcare, in terms of, for instance:**

- opening up access to expert second opinions
- seeking guidance on the best route to diagnosis
- advice on suitability of patients for specialised treatments including cutting-edge procedures and specialised surgery
- once panels are closed, if patients provided consent, their details can be retained in the CPMS (in a pseudonymised form) and the cases become searchable, for instance for educational purposes. Medical researchers can request access to data for research purposes

The route by which patient cases enter the CPMS seems somewhat varied. Clinicians from centres which are *not* members of the ERNs can be granted 'guest status' to give temporary access to the System to refer complex cases. The pathways for this seem to lack some clarity (e.g. it is not clear whether such patients must first be referred to an HCP in the same country, before calling upon the expertise of the ERN). Each ERN has experts granted particular types of user profiles, who perform a triage of sorts, in order to filter out cases which can be addressed without the need of a multi-expert and perhaps multidisciplinary panel. These experts then set-up panels and contact panellists for the cases which will go forwards (this person may be the coordinator or a dispatcher). Once the panel has been concluded, the patient will receive findings, recommendations and a treatment plan.

CPMS IN NUMBERS:

- **As of May 2019, 1268 active users are registered in the CPMS** (an 'active user' is an individual who has logged in at least once);
- **623 panels have been opened at some stage**
- **245 panels have been closed and archived.**

Ultimately, of course, any recommendation by an ERN expert panel that a patient should receive a particular treatment/procedure/medicinal product which is not usually available in their own country **does not automatically incur preferential consideration** for that patient to actually *access* said treatment/procedure/medicinal product: access remains subject to Regulation (EC) No 883/2004 on the coordination of national social security systems and to the Cross-Border Healthcare Directive 2011/24/EU.

3.4. Expansion of the ERNs and Integration into Health Systems

An important topic of direct relevance to the success of the ERNs is how best to integrate ERNs to national health systems. A key assumption of the ERN concept was that not every centre with expertise in a rare disease or a highly specialised procedure should be enrolled as a full member in an ERN; instead, the vision was to embrace a 'hub and spoke' model in which, perhaps, out of a dozen centres in any given country with expertise in a broad group of conditions, only one or two would actually become full members of that Network. Those centres would act as the national 'entry' points to each ERN, allowing a two-way exchange of knowledge, expertise, and -where necessary- patient cases.

Some countries found it challenging to choose such centres from amongst a relatively large pool. Other countries faced the opposite challenge: it was always acknowledged that smaller countries would struggle to find standalone centres of expertise able to meet the expert criteria necessary to join each of the 24 ERNs. In some cases, it would be possible to *build* capacity to allow centres to reach that requisite level of expertise, over time. For others, however, the size of the country alone would preclude this. **Nonetheless, for ERNs to realise their potential, it is essential for all European MS/EEA countries to be connected to the Networks in some meaningful way**. For this reason, the concept of 'affiliated' partners was born. There are three such categories, defined in the Legal Acts:

- Associated National Centres
- Coordination Hubs
- Collaborative National Centres

In 2019, MS indicated the number of 'affiliated' partners they wish to join the ERNs.

A second call for full member HCPs is anticipated in 2019. **Thus the current picture, in terms of membership and 'affiliation' to ERNs, is set to change rather dramatically.**

Nonetheless, increasing the **number** of member HCPs and implementing the system of 'affiliated' centres will not automatically equal full integration to the national systems. **It is crucial to determine how ERNs intersect with -and indeed optimise- existing national pathways for patients with a rare condition/patients requiring highly specialised expertise**; for instance, how do patients with complex cases requiring a CPMS review actually obtain this service? To which centres in the national territory should they first be referred? How do less specialised doctors/professionals/citizens know what types of rare disease expertise exist in-country and where this expertise can be found (and once this awareness exists, how can more direct pathways be created to guide patient 'journeys' from primary or secondary care?)

In recent months, various groups of stakeholders have sought to address this fundamental challenge.

The BoMS of ERNs has a Working Group on this subject, which recently produced a 'Statement on the Integration of the European Reference Networks to the healthcare systems of Member States.' This document was adopted by the full Board in its June 2019 meeting. It provides guidance around 5 topics: national rare disease plans/strategies and legal framework for ERN integration; patient care pathways;

referral systems to the ERNs; support by Member States to ERN Coordinators, full members and affiliated partners; and information on ERNs provided at Member States level. It is accompanied by an Annex which proposes practical steps to drive forward improvements in each of those 5 areas; for instance, excellent proposals appear under the first area of national plans/strategies for RD, such as:

- 'Include ERN Coordinators and/or ERN Members/ Affiliated Partners into policy-making bodies or realise another way to involve their expertise into policy-making'; and
- [create] 'Clear and if necessary legally defined procedures for the identification and designation of national Centers of Expertise'.

- In November 2018, EURORDIS (Rare Diseases Europe) issued a set of ***Recommendations on the Integration of ERNs into National Health Systems*** https://www.eurordis.org/publication/eurordis-recommendations-integration-european-reference-networks-national-health-systems-0

An essential group of actors in the 'Integration' debate are the managers of the hundreds of hospital units and centres of expertise currently directly involved in the ERNs. As Andrzej Rys recently explained "Hospital managers are a cornerstone of the whole ERN system. Only through their active support, particularly in terms of human resource management, will the specialists be able to dedicate part of their working time to the ERNs, either as a coordinator or as a member."

Given the specificities of rare diseases and the challenges acknowledged at European level, it is perhaps important to think of several forms of 'integration':

- Integrating ERNs to the National Health systems, as above;
- Promoting the provision of **Integrated**, multidisciplinary care via the HCPs (CEs) and 'affiliated' centres of which ERNs are composed. Integrated care is first and foremost concerned with reducing fragmentation in care and creating more seamless patient journeys, coordinating care with all necessary medical specialists, with the patient at the centre.
- For rare diseases, however, it has been acknowledged that 'multidisciplinary' care often needs to involve actors from disciplines outside of the traditional medical sphere: the consensus EUCERD recommendations on what comnstitues a Centre of Expertise for rare diseases emphasize the need to also **coordinate** care with **paramedical and social actors**, for instance (see further the Rare2030 Knowledge Base Summary 'Integrated, social, and holistic care for rare diseases').

4. E-HEALTH

The topic of **eHealth** was incorporated to the 2008 **Commission Communication on Rare Diseases: Europe's challenges (2008) [679 final]** in some detail, as follows:

"eHealth can contribute in a number of different ways to this area [i.e. rare diseases], in particular through:

- Electronic online-services developed by Orphanet and by other EU funded projects, are a clear demonstration of how Information and Communication Technology (ICT) can contribute to putting patients in contact with other patients and developing patient communities, to sharing databases between research groups, to collecting data for clinical research, to registering patients willing to participate in clinical research, and to submitting cases to experts which improve the quality of diagnoses and treatment;
- Telemedicine, the provision of healthcare services at a distance through ICT, is another useful tool. It can, for instance, enable to bring highly specialised expertise on rare diseases to ordinary clinics and practices, such as a second opinion from a centre of excellence
- Research funded under FP7 in the area of computer assisted modelling of physiological and pathological processes is a promising approach to help understanding better the underlying factors of rare diseases, predicting outcomes and possibly finding new treatment solutions."

In the decade since the adoption of the Commission Communication and Council Recommendation, ICT solutions have impacted significantly on the rare diseases field, most prominently perhaps through the aforementioned Clinical Patient Management System or CPMS. Countries continue to move to eHealth solutions, in favour of paper-based systems. Telemedicine tools to enable virtual consultations at a distance hold major potential, particularly for countries where patient populations are scattered and people live very far away from an appropriate centre of expertise.

An important body in the history of eHealth in Europe was the eHealth Network (eHN), established via Article 14 of the Cross-Border Healthcare Directive. The eHN oversaw the creation and evolution of a number of eHealth Digital Service Infrastructures or eHealth DSIs. This work has been funded within the framework of the Digital Europe Programme and can, in some sense, be considered to stem from (or at least was largely driven by) the epSOS initiative. Ending in 2014, epSOS ("Smart Open Services for European Patients") was a European large-scale pilot testing the cross-border sharing of

a) a patient's most important health data summary, intended for use in an unplanned (e.g. emergency) care situation when travelling or working abroad; and
b) b) an electronic prescription (ePrescription).

In the years since the epSOS project ended, multiple initiatives have sought to move forwards with the maturation and deployment of these two eHealth 'tools'. Whereas the ERNs are primarily concerned with ***planned*** cross-border care, the ePatient Summary and the ePrescription tool are designed for use in ***emergency*** care settings. A small TaskForce initiated under the EU Joint Actions for Rare Diseases has undertaken initial work with eHealth initiatives to highlight the need to consider rare disease patient needs in these two Digital Service Infrastructures.

In 2018 the *Commission Communication on enabling the digital transformation of health and care in the Digital Single Market; empowering citizens and building a healthier society* set out the Commission strategy to transform healthcare under the Digital Single Market. Specific proposals were geared around 3 areas, which may also be relevant to the issue of accessing healthcare :

1. **Citizens' secure access to their health data, also across borders**- enabling citizens to access their health data across the EU;
2. **Personalised medicine through shared European data infrastructure** - allowing researchers and other professionals to pool resources (data, expertise, computing processing and storage capacities) across the EU;
3. **Citizen empowerment with digital tools for user feedback and person-centred care** - using digital tools to empower people to look after their health, stimulate prevention and enable feedback and interaction between users and healthcare providers.

5. 2019 REPORT ON THE CROSS-BORDER HEALTHCARE DIRECTIVE

Directive 2011/24/EU, the oft-named Cross-Border Healthcare Directive, has initiated numerous activities across Europe of relevance to rare diseases and specialised healthcare. However, a recent report from the European Court of Auditors concluded that there is significant scope for improvement: "EU citizens still don't benefit enough from the ambitious actions set out in the Cross-Border Healthcare Directive. EU action includes the right to cross-border treatment, facilitating the exchange of patients' health data across borders, and initiatives for rare diseases; but better management is needed to deliver on these ambitions". Amongst the specific recommendations raised are the following (cited here as they are of particular relevance for this topic):

VI. *The Commission has overseen the implementation of the Cross-border Healthcare Directive well. It has guided the National Contact Points towards providing better information on cross-border healthcare, but there remains some scope for improvement.*

VII. *At the time of our audit, no exchanges of patients' data between Member States had taken place and no benefits to cross-border patients from these exchanges could be demonstrated. The Commission did not establish an implementation plan with timelines for its new eHealth strategy and did not estimate the volumes of potential users before deploying the cross-border health data exchanges.*

VIII. *The concept of European Reference Networks for rare disease is widely supported by EU stakeholders (patients' organisations, doctors and healthcare providers). However, the Commission has not provided a clear vision for their future financing and how to develop and integrate them into national healthcare systems.*

IX. Based on our conclusions, we make recommendations focusing on the Commission's support for National Contact Points, the deployment of cross border exchanges of health data, and EU's action in the field of rare diseases."

6. CLINICAL PRACTICE GUIDELINES AND CLINICAL DECISION SUPPORT TOOLS

Amongst the most powerful tools to generate and disseminate knowledge in the clinical and research settings are up-to-date clinical practice guidelines or clinical decision support tools (CDSTs, a broad term encompassing many types of guidance), which may be generated for a range of purposes, such as clinical diagnosis, management and treatment. High quality treatment pathways and clinical guidelines, as well as the presence of a core multidisciplinary team, are important prerequisites for improved clinical outcomes and ultimately survival and improved quality of life of patients living with a rare disease or rare cancer. Often a large number of clinical guidelines exist, but the implementation of and adherence to these evidence-based clinical guidelines is limited (in some cases, less than 40% of patient care is provided according to existing evidenced-based guidelines).

Clinical practice guidelines/CDSTs serve as a great equaliser in the RD field: they can mean the difference between no care/substandard care and patients living longer, healthier lives with fewer complications. Guidelines, whether designed to support diagnosis or care, can serve as a blueprint of excellence, to advise doctors closer to the patients on how to treat them in a way that reflects the best possible knowledge and will generate the best possible outcomes.

There is no specific section in the Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02) dedicated to CPGs/CDSTs; however, SECTION VI. 'GATHERING THE EXPERTISE ON RARE DISEASES AT EUROPEAN LEVEL' asked Member States to:

"**Gather national expertise on rare diseases and support the pooling of that expertise with European counterparts in order to support: (a) the sharing of best practices on diagnostic tools and medical care** as well as education and social care in the field of rare diseases; … (d) the development of European **guidelines** on diagnostic tests or population screening, while respecting national decisions and competences".

WHY DO GUIDELINES FOR RARE DISEASES AND HIGHLY SPECIALISED PROCEDURES REQUIRE A PARTICULAR APPROACH?

CPGs are traditionally generated in accordance with robust methodological approaches and are based upon a rich body of evidence (the pinnacle of which is usually assumed to be randomised controlled trials). Methodological approaches such as GRADE work well when there is strong data and evidence; however, such instruments typically require substantial adaptation for the rare disease field, where the published evidence is limited (generally speaking, the lower the prevalence of a rare disease, the lower the volume of published evidence). In such cases, alternative methodologies become very important and help to provide assurance for the development of Clinical Decision Support Tools, such as expert opinions and consensus statements.

The European Commission has invested in the topic of CPGs for rare diseases in a variety of ways:

1. The RareBestPractices project: this was an FP7 initiative, which developed a platform to collect and exchange infor**mation** on best practices for the management of rare diseases. Major outputs included the RareGUIDELINE and RareGAP databases

2. **Orphanet** established a procedure for the selection, quality evaluation and dissemination of CPGs, with the aim of providing easy access to relevant, accurate and specific recommendations for the management of RD. Orphanet also produces and disseminates Emergency Guidelines

3. Numerous disease-specific or disease-oriented projects and 'pilot' Networks were funded by DG SANTE in the 2nd and 3rd public health programmes with a focus on developing new CPGs/CDSTs (see for instance the summaries in Rare Diseases 2008-2016: EU funded actions paving the way to the European Reference Networks)

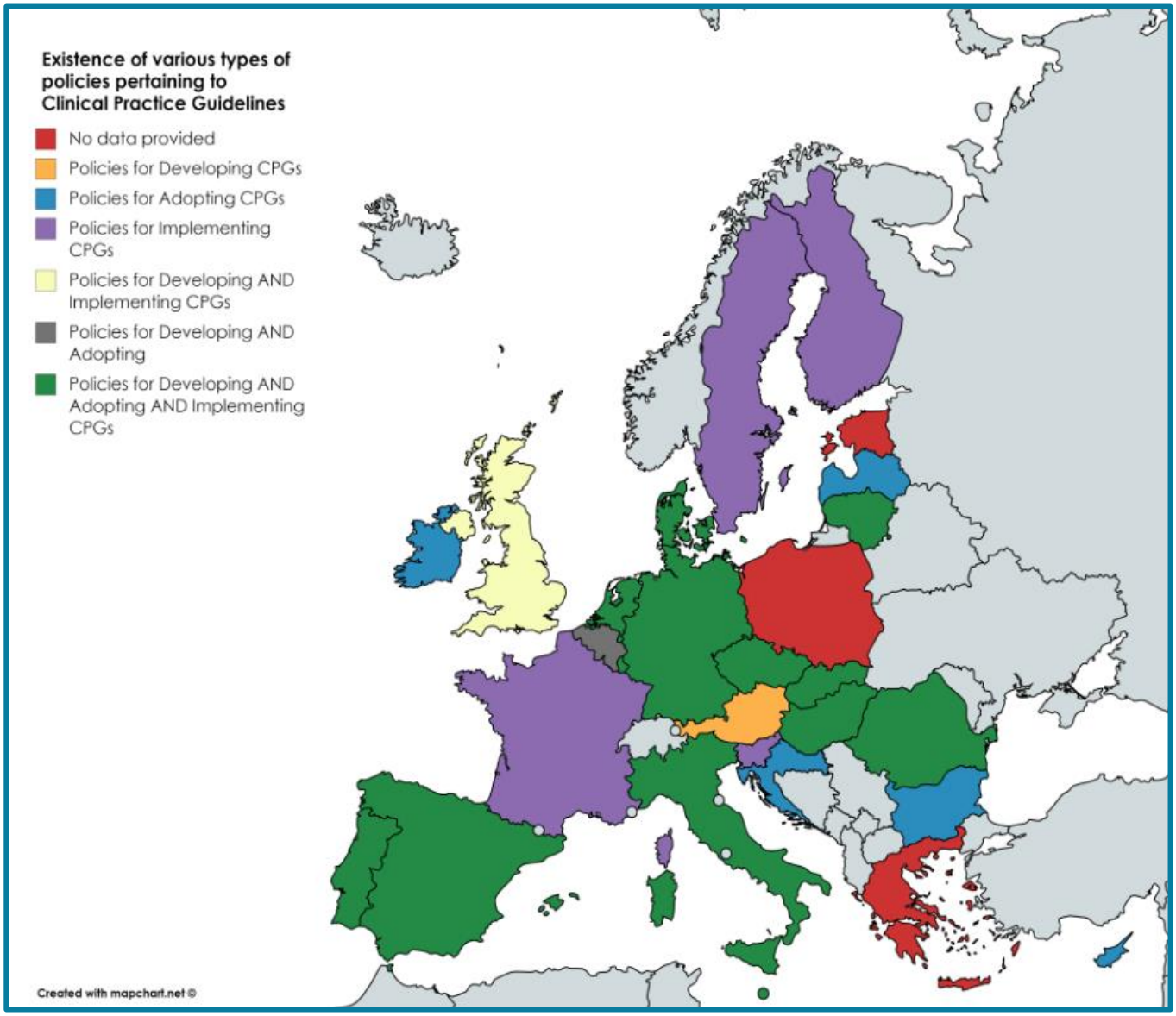
Historically, even where guidance has been generated for particular rare diseases/highly specialised procedures, countries have opted to implement this differently across Europe (indeed even within single countries). It has long been recognised that it would be useful to have a better understanding of national policies (where existing) for generating and using CPGs for rare diseases. To this end, the Data Contributing Committees providing information at the national level for the resource on the State of the Art of RD Activities in Europe, are asked to provide some data on this subject: countries are asked the following question: Has your country produced any CPGs for rare diseases at the national level?

Of 24 MS which responded, 18 stated that they have (although it is likely that this question requires more concrete definitions).

In accordance with the wording of the EUCERD Recommendations on Core Indicators for Rare Disease National Plans /Strategies, countries are also asked if they a national policy in place for…

- Developing;
- Adapting;
- Implementing;…

… Clinical Practice Guidelines. The status quo as of May 2019 appears quite heterogeneous, as shown in the map below (please note that a few countries have yet to update their data).



The EC ERN Delegated Decision, Annex 1, point 4(c) states that Networks "shall (...) develop and implement clinical guidelines and cross-border patient pathways" while Annex II, point 1(e)(iv) states that the healthcare providers applying to become members of the Networks "must (...) develop and use clinical guidelines and pathways in their area of expertise". **ERNs are well-placed to add value to the status quo** around generating, appraising, disseminating and -hopefully- using CPGs. If this potential is to be realised, countries will need assurance that guidelines emerging from the ERNs are of sufficient quality and methodological rigour for implementation at national level.

A Tender will be awarded in 2019, to support all 24 ERNs in generating and appraising CPGs/CDSTs, using common methodological procedures as far as possible.

7. TRAINING AND EDUCATION

The diagnosis, treatment and care of people with a rare disease typically demands particular knowledge and skills on the part of medical and social professionals. It is important to exchange good practices, at the clinical level, and to increase the quality of care: but at the same time, it is acknowledged that training and educating the *next* generation of professionals is essential in order to maintain the requisite focus and specialisation in rare and complex conditions in future. A few initiatives and organisation are addressing these challenges for the rare disease field, as summarised below (NB: trainings aimed at patient empowerment and partnerships, and trainings oriented towards holistic and social care are addressed in the respective Knowledge Base Summaries).

RESOURCE/INITIATIVE	MAIN GOALS/ACTIVITIES
Medics4RareDisease (M4RD)	**M4RD** provides education in the Rare Disease field for medical students and doctors in training. They have developed a number of resources that medical students and trainee doctors may find useful. These include: • A clinical and patient ambassador programme enabling M4RD to work with the wider rare disease community so we can learn from their expertise and experience. • A video and revision library to assist doctors with their studies and exams. • Events and conferences organised either organised by M4RD or where M4RD are represented. This includes an annual symposium. Overall, M4RD aims to improve the patient-doctor relationship and speed up the journey to diagnosis.
Union Européenne des Médecins Spécialistes (UEMS)	The UEMS consists of a Council and **43 Specialist Sections** representing medical practitioners in 40 countries. Representing over 1.6 million medical specialists, it is the oldest medical organisation in Europe. One of the modes of operation for UEMS are the Multidisciplinary Joint Committees (MJC). A primary aim of the MJCs is to certify the standards of education for physicians and other learners in order to promote patient safety. They also aim to advance the science of clinical education, training, and assessment in a multidisciplinary manner in sections with mutual interest. The MJCs also aim to create a system of support for the delivery of state of the art clinical skills training within the EU and EU affiliated countries There is now a Multidisciplinary Joint Committees for rare and undiagnosed disease.
European Joint Programme on Rare Diseases (EJPRD)	The **EJPRD** brings together over 130 institutions (including all 24 ERNs) from 35 countries to create a comprehensive, sustainable ecosystem allowing a virtuous circle between research, care and medical innovation. To achieve this end, the EJPRD actions are organized within major **Pillars: Pillar 3** is dedicated to Training and Empowerment and consists of four work packages:

	Management & Quality of Data – training activities are focused on the following topics: • Orphanet nomenclature and rare disease ontologies for RD research • Standards and quality of genetics/genomics data in laboratory and clinical research practice • Strategies to foster solutions for undiagnosed rare diseases cases • Sample data management in biobanks, RD Registries and FAIRification of data at the source and ERDRI. **Patient and Researcher Development** - providing an understanding of therapeutic development and developing the skills of patients to become collaborators in RD research. **ERN Training and Support Programme** - creating and implementing a comprehensive programme of education and empowerment for different stakeholders such as researchers and clinicians. Initiatives will include research mobility fellowships, training workshops and accreditation of individual workshops at institutions such as the UEMS. **Online Academic Education Course** - Ensuring that capacity building activities address the developing education and training needs of key stakeholders across Europe involved in RD research. This will include developing or adapting high quality e-learning modules, applicable to RD broadly (as opposed to disease-specific content), and providing transversal, multidisciplinary content.

8. RESULTS OF THE RARE 2030 LITERATURE REVIEW*

*The earlier sections of this document were elaborated via research, partner expertise, and data stemming from the Resource on the State of the Art of Rare Disease activities in Europe. This final section is a summary of the results of a literature review performed by INSERM Orphanet, and is designed to highlight peer-reviewed publications which may suggest trends in this broad topic.

The development of services and care dedicated to the treatment and acknowledgement of rare diseases within healthcare systems is not the only hurdle which needs to be overcome to adequately address the challenges that represent rare diseases in this field. Indeed, besides the common d**evelopment of research, clinical and care innovations**, it is necessary to assess and ensure the **accessibility and equity of these services**.

Unfortunately, the literature shows that patients and their caregivers face **many difficulties navigating healthcare pathways**. Many patients have to **wait for long periods of time before being provided specialised care suited to their condition** and are sent from one service to the other, what has been coined a **"diagnostic quest"** (Castro et al. 2017, Merker et al. 2018). They experience a fragmented infrastructure with very little guidance and suffer from the **lack of communication and coordination between health,**

social and local services (Castro et al. 2017). **A geographical barrier** is also often mentioned with the obligation for patients to travel long distances which might incur **significant costs** and act as a practical brake on the provision of specialised care (Fayet et al. 2018, Merker et al. 2018).

However, some trends offering solutions to these issues are currently observable. First, various types of **networking structures**, in Europe and elsewhere, are being designed and implemented in order to better **orient patients and improve the accessibility of existing services** (Castro et al. 2017; Fayet et al. 2018). For instance, in China, attention is paid to the development of a network of hospitals linking local, regional and national services and hospitals and fostering collaboration (Ren and Wang 2019; Soon et al. 2014); networking is also used as a means to improve access to rare cancer care (Frezza et al. 2019); some researchers positively assess the existence of non-profit foundation-sponsored clinic networks contributing to the deployment of specialised care (Merker et al. 2018); and in **Europe, the European Reference Networks have recently been set up**. These networks have been created to specifically resolve access inequalities (Wijnen et al. 2017) and aim to implement a multidisciplinary approach as a way to provide the most complete and holistic care possible. One trend observed with the establishment of this framework is therefore a move to establish a **European status for patients and hence a fundamental change in the vision and provision of healthcare services at the European level** (Ferrelli et al. 2017).

Another way to respond to the specific needs of the rare disease community is the implementation of **means to disseminate expertise and knowledge across long distances.** As such, European Reference Networks are creating a **'levelling-up' phenomenon of expertise with health professionals benefiting from the experience of their European colleagues.** Technological tools enabling remote care, such as telemedicine solutions, are also used (Merker et al. 2018). Many papers also emphasise the importance of **guidelines as a means to disseminate knowledge and consequently improve the accessibility of expert care and treatment** (Pai et al. 2019; Pavan et al. 2017; Fayet et al. 2018; Wijnen et al. 2017), as well as the need to consolidate health professionals' education on rare diseases (Fayet et al. 2018; Ramalle-Gomara et al. 2014).

Another aspect of the 'inequality in access' debate concerns the case of members of ethnically diverse communities **who are not referenced within genomic and phenotypic databases, such as certain indigenous peoples** (Baynam 2017). The **global effort towards universal health coverage is also very influential.** The emphasis on equity, quality, responsiveness, efficiency, and resilience should very likely contribute to a better inclusion of rare diseases in national health policy planning at the global level and hence improve accessibility levels (cf. UHC2030).

Finally, an additional trend is linked to the **economic environment and reduced health expenditure** which might very likely impact negatively on the rare disease field and on accessibility prospects for patients (Ferrelli et al. 2017). Hence, the literature review reveals the **need to re-evaluate the concept of fairness underlining the sharing of the health budget.** Rather than assessing budget allocation decisions according to purely economic considerations (most notably cost-effectiveness, priority to the worst-off and financial risk protection), one could pay more attention to **population social values and assess decisions via a citizen's perspective** (Richardson and Chandler 2019; Norheim 2016).

REFERENCES FROM THE RARE DISEASE LITERATURE REVIEW

FULL LIST OF ARTICLES / PUBLICATIONS FOUND IN THE LITERATURE REVIEW:

https://docs.google.com/spreadsheets/d/1SRXASsFiD9sdQz286SVo860XdTpGaOIncyjlhGphULI/edit#gid=364400914

SELECTED BIBLIOGRAPHY OR KEY PUBLICATIONS

- Baynam, G., Molster, C., Bauskis, A., Kowal, E., Savarirayan, R., Kelaher, M., Easteal, S., Massey, L., Garvey, G., Goldblatt, J., Pachter, N., Weeramanthri, T.S., Dawkins, H.J.S., 2017. Indigenous Genetics and Rare Diseases: Harmony, Diversity and Equity, in: Posada de la Paz, M., Taruscio, D., Groft, S.C. (Eds.), Rare Diseases Epidemiology: Update and Overview. Springer International Publishing, Cham, pp. 511–520. https://doi.org/10.1007/978-3-319-67144-4_27

- Castro, R., Senecat, J., de Chalendar, M., Vajda, I., Dan, D., Boncz, B., EURORDIS Social Policy Advisory Group 2017. Bridging the Gap between Health and Social Care for Rare Diseases: Key Issues and Innovative Solutions, in: Posada de la Paz, M., Taruscio, D., Groft, S.C. (Eds.), Rare Diseases Epidemiology: Update and Overview. Springer International Publishing, Cham, pp. 605–627. https://doi.org/10.1007/978-3-319-67144-4_32

- Fayet, Y., Coindre, J.-M., Dalban, C., Gouin, F., De Pinieux, G., Farsi, F., Ducimetière, F., Chemin-Airiau, C., Jean-Denis, M., Chabaud, S., Blay, J.-Y., Ray-Coquard, I., 2018. Geographical Accessibility of the Sarcoma Referral Networks in France. Intermediate Results from the IGéAS Research Program. IJERPH 15, 2204. https://doi.org/10.3390/ijerph15102204

- Ferrelli, R.M., De Santis, M., Egle Gentile, A., Taruscio, D., 2017. Health Systems Sustainability and Rare Diseases, in: Posada de la Paz, M., Taruscio, D., Groft, S.C. (Eds.), Rare Diseases Epidemiology: Update and Overview. Springer International Publishing, Cham, pp. 629–640. https://doi.org/10.1007/978-3-319-67144-4_33

- Frezza, A.M., Trama, A., Blay, J.-Y., Casali, P.G., 2019. Networking in rare cancers: What was done, what's next. European Journal of Surgical Oncology 45, 16–18. https://doi.org/10.1016/j.ejso.2018.03.030

- Merker, V.L., Dai, A., Radtke, H.B., Knight, P., Jordan, J.T., Plotkin, S.R., 2018. Increasing access to specialty care for rare diseases: a case study using a foundation sponsored clinic network for patients with neurofibromatosis 1, neurofibromatosis 2, and schwannomatosis. BMC Health Serv Res 18, 668. https://doi.org/10.1186/s12913-018-3471-5

- Norheim, O.F., 2016. Ethical priority setting for universal health coverage: challenges in deciding upon fair distribution of health services. BMC Med 14, 75, s12916-016-0624–4. https://doi.org/10.1186/s12916-016-0624-4

- Pai, M., Yeung, C.H.T., Akl, E.A., Darzi, A., Hillis, C., Legault, K., Meerpohl, J.J., Santesso, N., Taruscio, D., Verhovsek, M., Schünemann, H.J., Iorio, A., 2019. Strategies for eliciting and synthesizing evidence for guidelines in rare diseases. BMC Med Res Methodol 19, 67. https://doi.org/10.1186/s12874-019-0713-0

- Pavan, S., Rommel, K., Mateo Marquina, M.E., Höhn, S., Lanneau, V., Rath, A., 2017. Clinical Practice Guidelines for Rare Diseases: The Orphanet Database. PLoS ONE 12, e0170365. https://doi.org/10.1371/journal.pone.0170365

- Ramalle-Gómara, E., Ruiz, E., Quiñones, C., Andrés, S., Iruzubieta, J., & Gil-de-Gómez, J., 2014. General knowledge and opinion of future health care and non-health care professionals on rare diseases. Journal of Evaluation in Clinical Practice, 21(2), 198–201.https://doi:10.1111/jep.12281

- Ren, Q., Wang, J., 2019 Network established to collaborate on diagnosis and treatment of rare diseases in China: A strategic alliance backed by tiered healthcare is the key to the future. https://doi:10.5582/irdr.2019.01024

- Richardson, J., Schlander, M., 2019. Health technology assessment (HTA) and economic evaluation: efficiency or fairness first. Journal of Market Access & Health Policy 7, 1557981. https://doi.org/10.1080/20016689.2018.1557981

- Soon, S.-S., Lopes, G., Lim, H.-Y., Wong-Rieger, D., Bahri, S., Hickinbotham, L., Jha, A., Ko, B.-S., MacDonell, D., Pwu, J.R.-F., Shih, R., Sirachainan, E., Suh, D.-C., Wale, J., Zhang, X., Wee, H.-L., 2014. A call for action to improve access to care and treatment for patients with rare diseases in the Asia-Pacific region. Orphanet J Rare Dis 9, 137. https://doi.org/10.1186/s13023-014-0137-1

- Wijnen, R., Anzelewicz, S., Petersen, C., Czauderna, P., 2017. European Reference Networks: Share, Care, and Cure—Future or Dream? Eur J Pediatr Surg 27, 388–394. https://doi.org/10.1055/s-0037-1607057

Rare2030

Foresight in Rare Disease Policy

The health of 30 million people living with a rare disease in Europe should not be left to luck or chance. The Rare 2030 foresight study prepares a better future for people living with a rare disease in Europe by gathering the input of a large group of patients, practitioners and key opinion leaders to propose policy recommendations.

Since the adoption of the Council Recommendation on European Action in the field of Rare Diseases in 2009, the European Union has fostered tremendous progress to improve the lives of people living with rare diseases. Rare2030 will guide a reflection on rare disease policy in Europe through the next ten years and beyond.

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The Rare2030 project is co-funded by the European Union Pilot Projects and Preparatory Actions Programme (2014-2020). This leaflet is part of the pilot project PP-1-2-2018-Rare 2030. The content represents the views of the author only and is his/her sole responsibility; it cannot be considered to reflect the views of the European Commission or any other body of the European Union.

This document was elaborated by Rare 2030 WP4, under the leadership of Newcastle University and with input from all partners. The document should be referenced as follows: Hedley, V. and Rodwell, C. (2019) *Rare 2030 Knowledge Base Summary on Access to Healthcare for Rare Diseases* https://www.rare2030.eu/our-work/