TOOL 3

What are ERNs?

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Key Messages

European Reference Networks (ERNs) are arguably the single most important innovations in health and research for rare diseases in Europe, if not globally.

☑ There are 24 ERNs, launched in 2017, established across broad rare disease groups such as rare liver diseases, rare eye disease, etc., or are dedicated to areas of highly specialised medicine such as paediatric transplantation

☑ ERNs are networks connecting EU/EEA centres of expertise in specialised healthcare fields necessitating a concentration of expertise

☑ At present, they bring together 1613 Healthcare Providers/centres/units, nested in 382 separate hospitals across all 27 EU Member States plus Norway

☑ The primary focus of ERNs is improving care, and the networks are officially coordinated under the European Commission Directorate General concerned with Health (DG SANTE). However, they have strong research responsibilities and priorities too, offering enormous potential

☑ ERNs are designed to be patient-centred, with patients embedded in the governance and in all activities – this is facilitated by the concept of ePAGs (European Patient Advocacy Groups). Today, there are over 300 ePAGs working with ERNs

☑ The Clinical Patient Management System (CPMS), a secure digital platform used by the ERNs, has enabled the virtual consultation of more than 4000 complex cases

☑ Over 95,000 patients have already been included in the dedicated new ERN registries

The Road to ERNs

The first formal call for ERNs was launched back in 2016, representing over a decade of preparatory work by so-called 'pilot' ERNs.[1] A significant amount of planning lay behind that milestone moment, driven by the European Expert Groups for Rare Disease (EUCERD and the Commission Expert Group on Rare Disease), Joint Actions (the EUCERD Joint Action and RD-ACTION, in particular) and, crucially, advocacy from patient organisations, most notably EURORDIS. A model of possible disease groupings was developed,[2] to help avoid hundreds -or even thousands - of applications seeking to set-up ERNs in individual diseases or small, clinically distinct groups of diseases. RD-ACTION worked with the European rare disease community to help ensure that each community would rally behind only one application, to avoid competing proposals and try to ensure all rare diseases could be categorised under at

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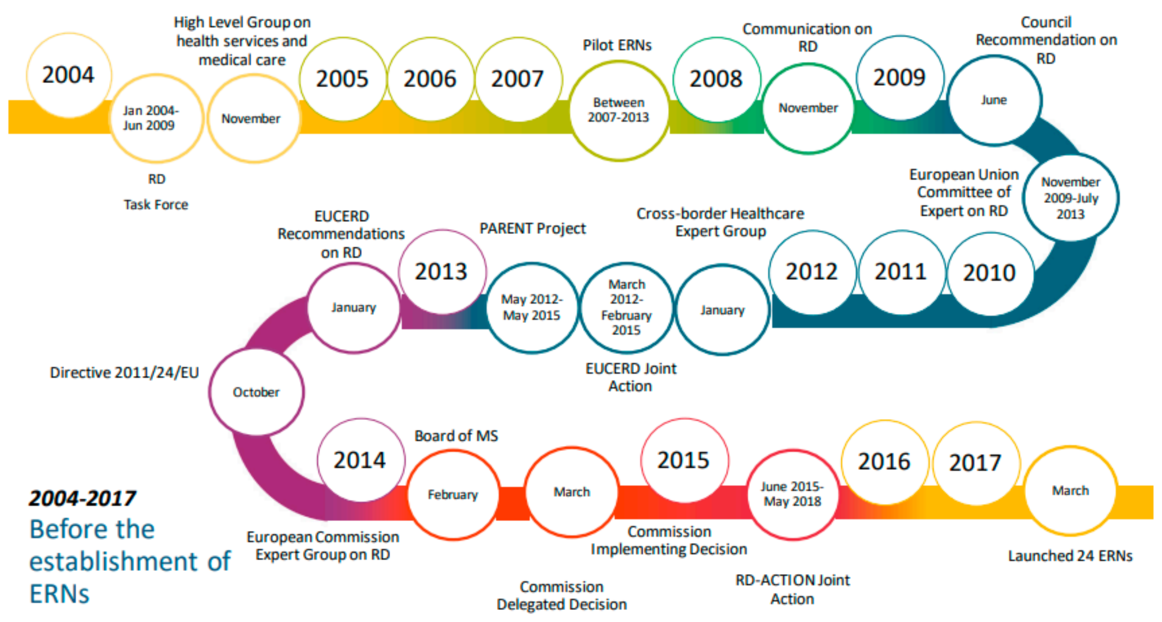
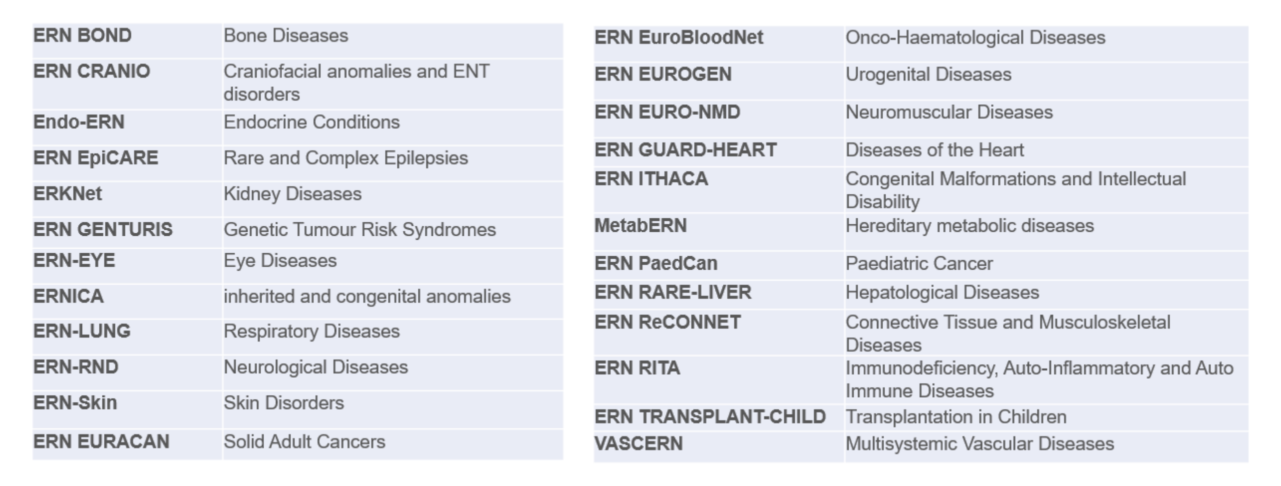
[1] European Commission, Consumers, Health, Agriculture and Food Executive Agency, Rare diseases 2008-2016 : EU-funded actions paving the way to the European reference networks, Publications Office, 2018, https://data.europa.eu/doi/10.2818/578367

[2] https://ojrd.biomedcentral.com/articles/10.1186/s13023-016-0398-y



Source: ECA.

Fig. 1 - Successive policy developments leading to the launch of the ERNs (Image from the European Court of Auditors Report on the Implementation of Directive 2011/24/EU)



ERN BOND	Bone Diseases
ERN CRANIO	Craniofacial anomalies and ENT disorders
Endo-ERN	Endocrine Conditions
ERN EpiCARE	Rare and Complex Epilepsies
ERKNet	Kidney Diseases
ERN GENTURIS	Genetic Tumour Risk Syndromes
ERN-EYE	Eye Diseases
ERNICA	inherited and congenital anomalies
ERN-LUNG	Respiratory Diseases
ERN-RND	Neurological Diseases
ERN-Skin	Skin Disorders
ERN EURACAN	Solid Adult Cancers
ERN EuroBloodNet	Onco-Haematological Diseases
ERN EUROGEN	Urogenital Diseases
ERN EURO-NMD	Neuromuscular Diseases
ERN GUARD-HEART	Diseases of the Heart
ERN ITHACA	Congenital Malformations and Intellectual Disability
MetabERN	Hereditary metabolic diseases
ERN PaedCan	Paediatric Cancer
ERN RARE-LIVER	Hepatological Diseases
ERN ReCONNET	Connective Tissue and Musculoskeletal Diseases
ERN RITA	Immunodeficiency, Auto-Inflammatory and Auto Immune Diseases
ERN TRANSPLANT-CHILD	Transplantation in Children
VASCERN	Multisystemic Vascular Diseases

Fig. 2 – The 24 ERNs

least one of these networks.[3] The 24 Networks were officially launched in 2017.

In the end, their headings largely reflected the proposed model of disease grouping, with a few logical modifications to incorporate not only classifications of pathology but also areas of highly specialised healthcare which span across diseases. This was important, to achieve a central pillar of the ERN vision - collectively, across all ERNs, every rare disease should have a 'home'. Cross-ERNs collaborations would also facilitate the need for multidisciplinary expertise when dealing with rare or ultra rare diseases. In this way, ERNs would strive to go beyond the networks created by past EU funding, via projects, which were dedicated to individual diseases or small groups of diseases, and would instead seek to improve diagnostics, treatment, research and care for all conditions under the rare disease umbrella. A further fundamental difference here was that ERNs are not projects – subject to 5-yearly evaluations, these Networks should be considerer permanent structures, revolutionising rare disease care and research across Europe.

At their launch, the 24 ERNs brought together over 900 specialist units in over 300 hospitals across 26 countries (25 EU MS plus Norway). These figures have increased in subsequent years (see 'Getting to know the ERNs' below), to include 1613 members, in total.

ERNs, as cross-border networks, have many substantial responsibilities, spanning the care and research domains. The tables below collate a non-exhaustive set of resources which:

- ☑ further explain the origins of the ERNs
- ☑ provide analysis/recommendations for their future functioning
- ☑ and illustrate the status quo across the Networks.

Key resources outlining the scope, nature and achievements of the ERNs

Origins of the ERNs – the concept, the criteria, the Legal Acts and the background

Title	Type of Resource	Summary of what you can find	Link
EUCERD Recommendations on Rare Disease European Reference Networks	**Grey literature/ reports/ recommendations**	Foundational recommendations on what ERNs should be and should do, adopted unanimously by the EU Committee of Experts on Rare Disease (EUCERD) on 31st January 2013. Incorporated and reflected past learnings from the field and formed the basis for the legislation which followed	https://www.rd-action.eu/eucerd/EUCERD_Recommendations/ern_recos.pdf
European Reference Networks for rare diseases: what is the conceptual framework?	**Peer-Reviewed Publication**	Héon-Klin, V. European Reference networks for rare diseases: what is the conceptual framework?. Orphanet J Rare Dis 12, 137 (2017). https://doi.org/10.1186/s13023-017-0676-3 Presents a comprehensive overview of the story behind ERNs	https://doi.org/10.1186/s13023-017-0676-3
Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare	**EU legislation**	This is the so-called 'Cross-Border Healthcare Directive; the legislation on which the ERNs were established (Art.12)	https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32011L0024
COMMISSION DELEGATED DECISION of 10 March 2014 (2014/286/EU)	**EU legislation**	The Delegated and Implementing Acts (see below) form the key legal basis for the creation and governance of ERNs. The Delegated Decision sets out core criteria and conditions that ERNs, and healthcare providers wishing to join an ERN, must fulfil	https://eur-lex.europa.eu/eli/dec_del/2014/286/oj/eng
COMMISION IMPLEMENTING DECISION on 10th March 2014 (2014/287/EU)	**EU legislation**	Accompanying the Delegated Acts, above, this legislation set out the formal criteria for establishing and evaluating ERNs and their Members, and for facilitating the exchange of information and expertise on establishing and evaluating the Networks	https://eur-lex.europa.eu/eli/dec_impl/2014/287/oj/eng
EC Consumers Health Agriculture and Food Executive Agency. Rare diseases 2008-2016: EU-funded actions paving the way to the European reference networks	**Grey literature/ reports/ recommendations**	Grey literature/ reports/ recommendations	European Commission: Consumers, Health, Agriculture and Food Executive Agency, Rare diseases 2008-2016 – EU-funded actions paving the way to the European reference networks, Publications Office, 2018, https://data.europa.eu/doi/10.2818/578367
Rare Disease European Reference Networks: Addendum to EUCERD Recommendations of January 2013	**Grey literature/ reports/ recommendations**	Addendum issued by the Commission Expert group on Rare Disease (successor to the EUCERD) to supplement the original 2013 Recommendations. Provides further detail on 1) meaningful patient involvement and patient-centredness in ERNs; and 2) a proposed disease-grouping model to ensure comprehensive coverage of ERNs	https://health.ec.europa.eu/publications/rare-disease-european-reference-networks-addendum-eucerd-recommendations-january-2013_en

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[3] https://tinyurl.com/43h3n63e

Rare 2030 Knowledge Base Summary on 'Access to Healthcare'	**Grey literature/ reports/ recommendations**	This was the eighth in a series of 'knowledge base summaries', essentially status-quo documents, published by the first foresight study for rare disease, Rare2030, in 2019. Section 3 summarises the background to ERNs, and lists some early achievements. It also includes a focus on the related concept of centres of expertise (section 2)	https://www.rare2030.eu/knowledgebase/
Overview Report on the State of the Art of Rare Disease Activities in Europe, 2018 Version	**Grey literature/ reports/ recommendations**	This large report summarises the status quo of a broad range of key topics related to rare disease, based on data and research collected in 2018. Section 5 is dedicated to the rise and early activities of ERNs and provides good background to the early years.	https://www.rd-action.eu/wp-content/upl

Analysis of the ERNs To-Date – Evaluations, Recommendations, Statements

Title	Summary of what you can find	Link
Tumiene, Birute et al. "European Reference Networks: challenges and opportunities." Journal of community genetics vol. 12,2 (2021): 217-229. doi:10.1007/s12687-021-00521-8	Journal article by many key people closely involved in ERNs. Analyses the ERN progress and vision comprehensively, and identifies challenges to the Networks fulfilling their potential	https://pubmed.ncbi.nlm.nih.gov/33733400/
Kole A, and Hedley, V,. Recommendations from the Rare 2030 Foresight Study: The future of rare diseases starts today (2021)	Full Recommendations published in 2021, emerging from the first foresight study for rare disease. Created through the input of over 250 experts from all stakeholder groups, these Recommendations cover a very broad range of topics, and include a section dedicated mainly to recommendations concerning ERNs (section 3 p.49 onwards). Useful for understanding how and where the RD community sees a need for ERN evolution and support	https://download2.eurordis.org/rare2030/Rare2030_recommendations.pdf
ERNs evaluation results report - Independent Evaluations of European Reference Networks and of Healthcare Providers	Official report published in 2024 and commissioned by the European Commission, to fulfil the legal requirement for ERNs and their member HCPs, to be evaluated every 5 years. The report presents a mix of self-evaluations, document reviews, ERN interviews, on-site HCP audits and stakeholder interviews. The results showed a high level of commitment of ERNs to their objectives, with a significant proportion (100% of ERNs and 89.7% of their members) achieving satisfactory results in the evaluation. The report shows areas of strength, as well as areas where improvements were recommended.	https://health.ec.europa.eu/latest-updates/erns-evaluation-results-report-independent-evaluations-european-reference-networks-and-healthcare-2024-11-29_en
Recommendations to Achieve a Mature ERN System in 2030	Recommendations generated by EURORDIS, reflecting the perspectives of their member patient groups and individual ePAGs, on the vision for a mature ERN system - reflects what patients feel is needed for these Networks to fulfil their potential	https://download2.eurordis.org/documents/pdf/Our_vision_on_mature_ERNs.pdf
Hedley, V., Bolz-Johnson, M., Hernando, I. et al. Together4RD position statement on collaboration between European reference networks and industry. Orphanet J Rare Dis 18, 272 (2023). https://doi.org/10.1186/s13023-023-02853-9	Peer-reviewed Position Statement addressing many key issues: outlining the historical reasons for limited ERN and Industry collaboration; explaining the work of Together4RD to improve the status quo; presenting case studies, precedents and ways of working between public and private sectors; and presenting recommendations to advance collaborations. This Statement includes many publications relevant for specific topics such as virtual care practices in ERNs, examples of ERN approaches to establishing new registries, etc.	https://doi.org/10.1186/s13023-023-02853-9
Statement of the ERN Board of Member States on Integration of the European Reference Networks to the healthcare systems of Member States.	Board of Member States Statement from 2019, proposing 5 ways in which ERNs need to be better integrated to national health systems	https://health.ec.europa.eu/system/files/2019-07/integration_healthcaresystems_en_0.pdf
Statement of the ERN Board of Member States on European Reference Networks and industry.	The first Statement on this topic, issued in 2016.	https://health.ec.europa.eu/document/download/1ea98fa6-10be-4a84-bb79-ba7678efc8bf_en?filename=2016_statement_industry_conflictofinterest_en.pdf
Updated Statement of the ERN Board of Member States on ERNs and industry.	This is an updated Statement from the Board of Member States, issued in June 2019	https://health.ec.europa.eu/system/files/2020-03/statement_industry_conflictofinterest_en_0.pdf

Getting to know the Networks – the Status Quo

The **official website of the ERNs under the European Commission** contains a lot of information about the Networks as a whole, the role of the Board of Member States of ERNs (which is the main executive oversight body for the ERNs), links to important official documents, etc. It is also a good place to learn more about any single Network, through **factsheets** (see for example **Figure 3**) and links to the individual ERN websites. Several of the specific resources highlighted below can be found from this main page.

European Commission | European Reference Networks

Working for patients with rare, low-prevalence and complex diseases

ERN on endocrine conditions (Endo-ERN)

Rare endocrine conditions include too much, too little or inappropriate hormonal activity, hormone resistance, tumour growth in endocrine organs, and diseases with consequences for the endocrine system. The epidemiological distribution is highly variable, spanning ultra-rare, rare and low-prevalence conditions. Patients with a low-prevalence disorder may require highly specialised care from a multidisciplinary team led by an endocrinologist.

The network has established eight main thematic groups covering the full spectrum of congenital and acquired conditions. These are: adrenal disorders; disorders of calcium and phosphate homeostasis; disorders of sex development and maturation; genetic disorders of glucose and insulin homeostasis; genetic endocrine tumour syndromes, disorders of growth and genetic obesity syndromes; hypothalamic and pituitary conditions; and thyroid disorders.

Endo-ERN continues to build on the work of several pre-existing European networks, including those established through the European Society of Endocrinology (ESE) and the European Society for Paediatric Endocrinology (ESPE), and those developed through European Cooperation in Science and Technology (COST) actions.

Aiming to deliver improved diagnostic trajectories, treatment, quality of care and measurable outcome for patients with rare endocrine conditions, Endo-ERN facilitates multidisciplinary and cross-border collaboration in complex care, research and education, whilst ensuring patients' voices are heard.

NETWORK COORDINATOR
Professor Alberto M. Pereira
Amsterdam University Medical Center, Amsterdam, The Netherlands

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Fig. 3 - Example factsheet

A very useful resource is a new report published by the European Commission in March 2025: "**European Reference Networks: A success story for patients living with a rare disease**". This report presents the most recent stats on each ERN – detailing how many centres are engaged in ERNs at present. Following the initial call in 2016, which invited proposals for both the creation of ERNs and for constituent individual health care providers (HCPs) (including entire clinics, hospitals or specialised units within a larger institution), a second call was launched in 2019, with new members integrated in 2021.

Today, the 24 ERNs unite **1418 centres/units as full members, and an additional 195 members across two categories of formal 'affiliation' status** (these are centres which do not fulfil all horizontal and disease-specific criteria established by the European Commission and ERNs themselves, respectively, but will enable every country to access the expertise of an ERN more readily). **This gives a total of 1613 members, nested in 382 separate hospitals across all 27 EU Member States plus Norway.**

European Commission

Rare Diseases

European Reference Networks

A success story for patients living with a rare disease

Fig. 4 - https://health.ec.europa.eu/document/download/9bb51ea9-9d5a-4df7-9a9e-ee58cda21a0c_en?filename=ern_success-story_booklet_en.pdf

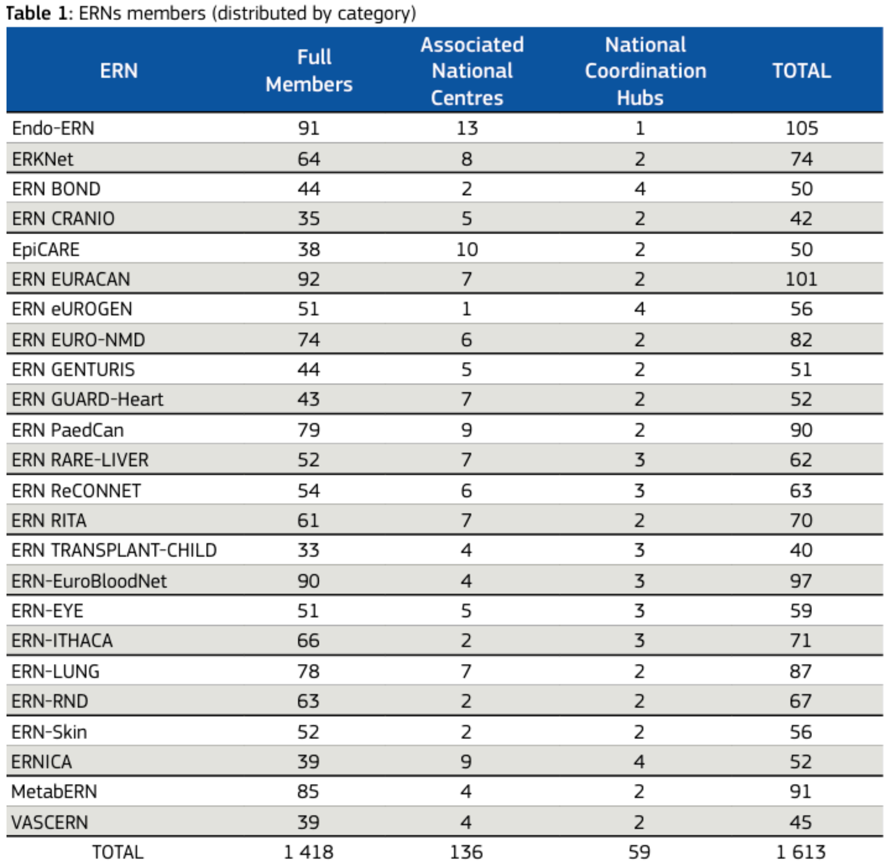


Table 1: ERNs members (distributed by category)

ERN	Full Members	Associated National Centres	National Coordination Hubs	TOTAL
Endo-ERN	91	13	1	105
ERKNet	64	8	2	74
ERN BOND	44	2	4	50
ERN CRANIO	35	5	2	42
EpiCARE	38	10	2	50
ERN EURACAN	92	7	2	101
ERN eUROGEN	51	1	4	56
ERN EURO-NMD	74	6	2	82
ERN GENTURIS	44	5	2	51
ERN GUARD-Heart	43	7	2	52
ERN PaedCan	79	9	2	90
ERN RARE-LIVER	52	7	3	62
ERN ReCONNET	54	6	3	63
ERN RITA	61	7	2	70
ERN TRANSPLANT-CHILD	33	4	3	40
ERN-EuroBloodNet	90	4	3	97
ERN-EYE	51	5	3	59
ERN-ITHACA	66	2	3	71
ERN-LUNG	78	7	2	87
ERN-RND	63	2	2	67
ERN-Skin	52	2	2	56
ERNICA	39	9	4	52
MetabERN	85	4	2	91
VASCERN	39	4	2	45
TOTAL	1 418	136	59	1 613

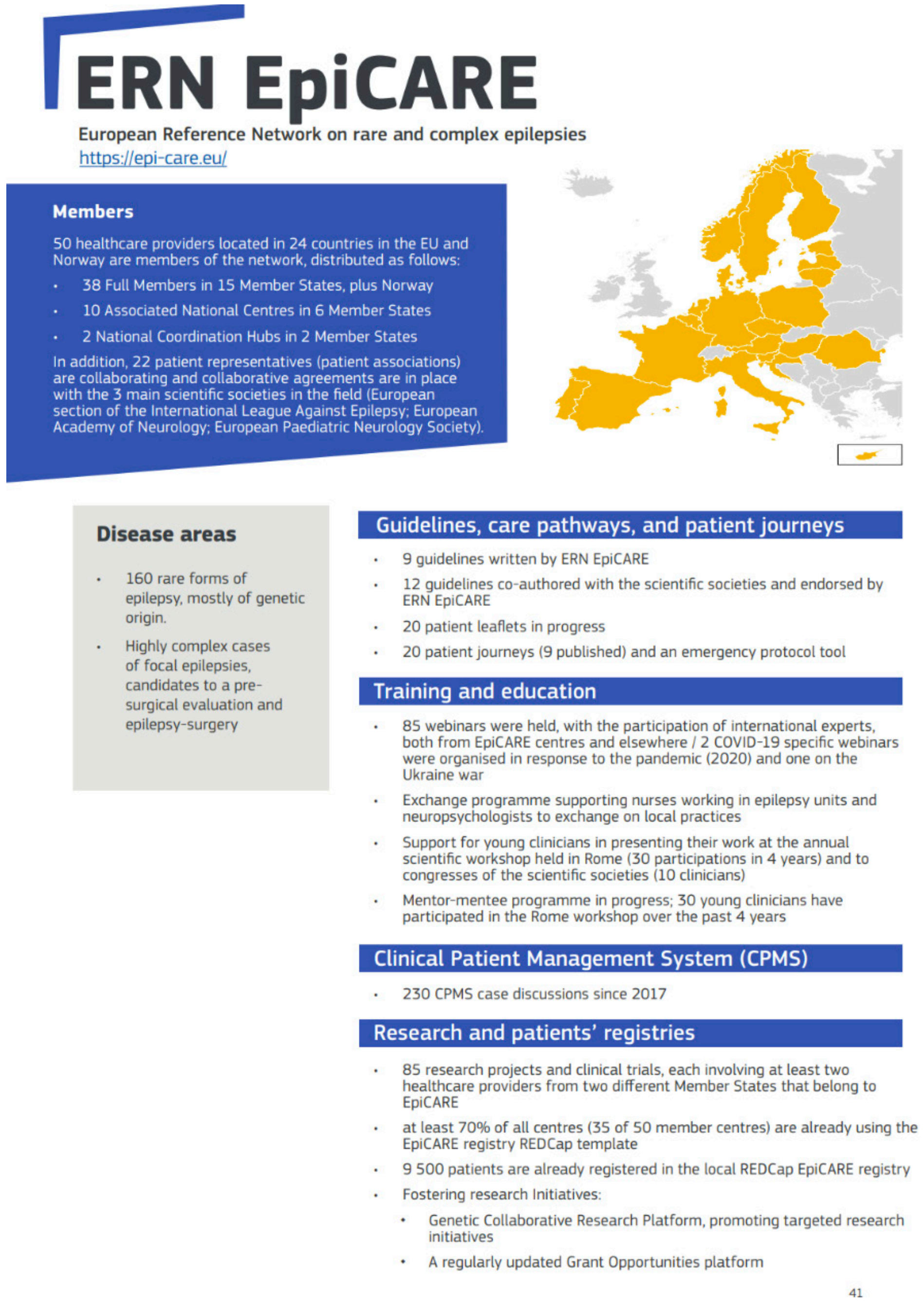
When compiling the information provided by each ERN, as summarised in this 2025 Report, several impressive statistics emerge; for instance:

- ☑ The networks range in size from 42 to 105 HCPs, with seven of them engaging over 80 HCPs each.
- ☑ Use of the CPMS for virtual consultations varies from a small number of consultations per ERN to over 500, with a total of over **4000 complex cases reviewed to-date**.
- ☑ **Over 170 clinical guidelines or clinical decision support tools have been written by the ERNs, collectively**, a figure which, when adding-in guidelines co-authored with ERN HCPs or endorsed by the Networks, rises to **over 590 resources**.
- ☑ **Over 95,000 patients** are registered across the new ERN registries, based on the estimates provided here by each Network.

This 2025 report also presents case studies showcasing the most effective and innovative achievements of the Networks, for instance;

- ○ activities in support of patients in Ukraine
- ○ efforts to make medicines available to patients in times of supply shortages

- reactiveness under the Covid-19 pandemic.



ERN EpiCARE

European Reference Network on rare and complex epilepsies
https://epi-care.eu/

Members

50 healthcare providers located in 24 countries in the EU and Norway are members of the network, distributed as follows:

- 38 Full Members in 15 Member States, plus Norway
- 10 Associated National Centres in 6 Member States
- 2 National Coordination Hubs in 2 Member States

In addition, 22 patient representatives (patient associations) are collaborating and collaborative agreements are in place with the 3 main scientific societies in the field (European section of the International League Against Epilepsy; European Academy of Neurology; European Paediatric Neurology Society).

Disease areas

- 160 rare forms of epilepsy, mostly of genetic origin.
- Highly complex cases of focal epilepsies, candidates to a pre-surgical evaluation and epilepsy-surgery

Guidelines, care pathways, and patient journeys

- 9 guidelines written by ERN EpiCARE
- 12 guidelines co-authored with the scientific societies and endorsed by ERN EpiCARE
- 20 patient leaflets in progress
- 20 patient journeys (9 published) and an emergency protocol tool

Training and education

- 85 webinars were held, with the participation of international experts, both from EpiCARE centres and elsewhere / 2 COVID-19 specific webinars were organised in response to the pandemic (2020) and one on the Ukraine war
- Exchange programme supporting nurses working in epilepsy units and neuropsychologists to exchange on local practices
- Support for young clinicians in presenting their work at the annual scientific workshop held in Rome (30 participations in 4 years) and to congresses of the scientific societies (10 clinicians)
- Mentor-mentee programme in progress; 30 young clinicians have participated in the Rome workshop over the past 4 years

Clinical Patient Management System (CPMS)

- 230 CPMS case discussions since 2017

Research and patients' registries

- 85 research projects and clinical trials, each involving at least two healthcare providers from two different Member States that belong to EpiCARE
- at least 70% of all centres (35 of 50 member centres) are already using the EpiCARE registry REDCap template
- 9 500 patients are already registered in the local REDCap EpiCARE registry
- Fostering research Initiatives:
  - Genetic Collaborative Research Platform, promoting targeted research initiatives
  - A regularly updated Grant Opportunities platform

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Fig. 5 - Example of an ERN summary in the 2025 report 'ERNs: A success story for patients living with a rare disease'

This 2025 report also presents case studies showcasing the most effective and innovative achievements of the Networks. Although only established in 2017, the ERNs have proven themselves highly agile and reactive in times of crisis:

- ☑ Only a few weeks after the onset of the COVID-19 pandemic, nearly all ERNs organised webinars during which experts provided concrete advice, to both patients with rare diseases and their treating physicians, on how to deal with drug suppliance/ shortage, drug interactions, risks in using -or not using- antivirus treatments, indications and safety related to vaccinations, and quality of life issues related to "stay-at-home" decisions. In partnership with their respective scientific societies they also produced several peer reviewed recommendations.
- ☑ Similarly, when Ukraine was invaded, the ERNs offered support to doctors working in the country or to refugees in EU countries. For instance, **a dedicated website** provided contact details for each of the 24 ERNs.

The resources highlighted in the table below (which include this recent European Commission report) are ERN-agnostic, and are intended to introduce the status quo at the cross-ERN level. The best way to learn about the achievements and what is happening in each individual Network is to visit **their individual websites**, which will link to publications, training materials, the registries established by each, and much more.

Title	Summary of what you can find	Link
European Reference Networks - 2023 presentation booklet	An official brochure, updated in 2023, which provides a brief overview of every ERN	https://health.ec.europa.eu/publications/european-reference-networks-2023-presentation-booklet_en
Factsheets for individual ERNs	You can download a factsheet for each of the 24 ERNs explaining, for instance, a little about the conditions under that heading, who the coordinator is, what clinically-distinct subgroups the Network is composed of. See fig. 3	https://health.ec.europa.eu/rare-diseases-and-european-reference-networks/european-reference-networks_en#the-24-european-reference-networks
European Reference Networks: A success story for patients living with a rare disease	An official report published by the European Commission in March 2025, presenting the most recent stats on each ERN – detailing how many centres are engaged in ERNs at present, for instance. The report has a stats page for each Network, covering achievements in areas such as CPMS (virtual referrals), registration of patients, training & education materials, guidelines, and more. The report also presents patient case studies, showing how ERNs have made a difference, and includes particular highlights from across the ERNs as a whole, such as support for Ukraine, collaborations across multiple ERNs, achievements in creating Postgraduate degree programmes, etc.	https://health.ec.europa.eu/latest-updates/booklet-european-reference-networks-success-story-patients-living-rare-disease-2025-02-24_en

A video on the ERNs	An official video created by the European Commission. This one is focused on explaining ERNs to patients and healthcare professionals	https://audiovisual.ec.europa.eu/en/video/I-193046
Websites for individual ERNs	This website provides direct links to the websites of each ERN. These sites provide a lot of information on the structure of the ERN, the governance, the centres who are members/associated partners, news & events, key resources, and much more	https://health.ec.europa.eu/rare-diseases-and-european-reference-networks/european-reference-networks_en#the-24-european-reference-networks
Downloadable zip-folder - List of Centres which are officially involved in each ERN	A means of searching for all centres which are formally part of any given ERN	https://health.ec.europa.eu/rare-diseases-and-european-reference-networks/european-reference-networks_en#the-24-european-reference-networks
Downloadable zip-folder - List of centres in each country which are formally involved with ERNs	A means of searching to see which centres in any given EU or EEA country are members of any ERN (and which one/ones they are part of)	https://health.ec.europa.eu/rare-diseases-and-european-reference-networks/european-reference-networks_en#the-24-european-reference-networks
Webinar - ERNs: a key EU infrastructure to partner for research activities, the why and the how	A webinar organised by Together4RD and the ERICA project (supporting ERN research), designed to introduce ERNs to anyone unfamiliar with them. A further goal is to bridge the knowledge gaps between ERNs and the pharmaceutical and biotech industries, fostering collaborations that can accelerate research and development in rare diseases, ultimately benefiting patients and advancing medical science	https://together4rd.eu/erns-a-key-eu-infrastructure-to-partner-for-research-activities-the-why-and-the-how/
Deliverable from ERICA – Monitoring Report on ERN Registries (2024)	This report was created by the Work Package on Data Collection, Integration and Sharing, and was last updated in Q1 of 2024. It summarises the different approaches and progress of ERNs around their registries, including type of registry (centralised, federated or hybrid); approaches to managing consent; data dictionary sizes, and types of data elements collected; HCP participation in ERN registries; cumulative records across all ERNs; and more.	https://erica-rd.eu/wp-content/uploads/2024/11/ERICA_D2.5_02_24_NEW.pdf
Publication on ERNs' support for Ukraine	A publication in The Lancet highlighting the role of the ERNs in responding to the crisis in Ukraine	https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(22)00160-0/fulltext

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RARE DISEASES

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