# Neurological Disorders and the European Reference Networks

**Presentations by:**

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# The WHO Global Action Plan on epilepsies & other neurological disorders: ERN EpiCARE, a partner of "neuro" ERNs


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*Member of the Executive Committee of ILAE – Europe*

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*Barcelona, Spain*


EpiCARE

UNIVERSITAT DE BARCELONA

European Reference Network


Co-funded by the European Union


SJD Sant Joan de Déu Barcelona · Hospital

# An historical WHO resolution


World Health Organization

**SEVENTY-THIRD WORLD HEALTH ASSEMBLY**
**Agenda item 11.6**

**A73/A/CONF./2**
**9 November 202**

## Global Actions on epilepsy and other neurological disorders

**Draft resolution proposed by Belarus, Bhutan, China, Colombia, Eswatini, the European Union and its Member States, Guyana, Iceland, Jamaica, Philippines, Russian Federation**

World Health Organization

# The creation of 24 ERNs : Common Areas of disease/ Thematic Networks

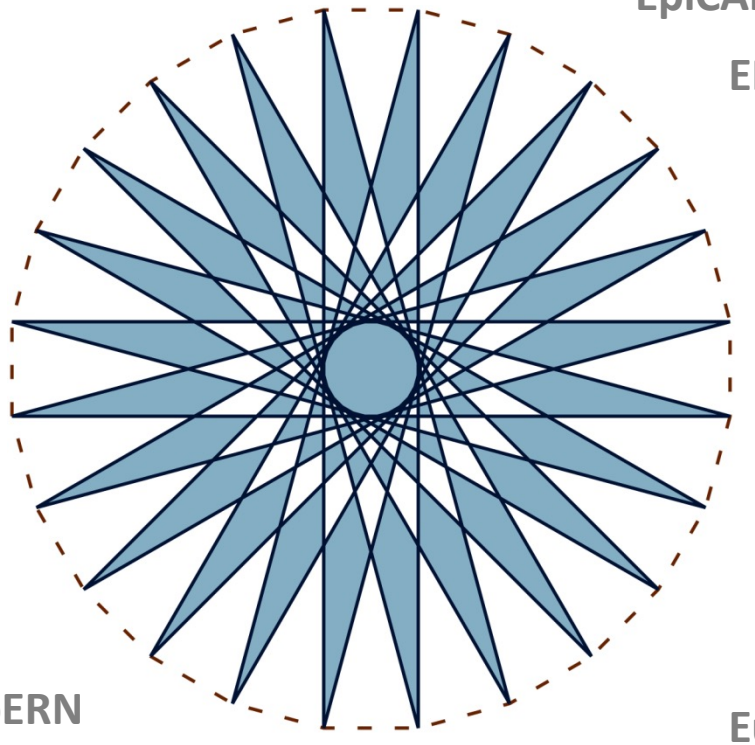
## The EU model

World Health Organization

- sharing expertise
- developing clinical research
- Supporting national networks
- sharing of best practices
- Partnership with patient advocates

World Health Organization
European Region

CRANIO
Endo-ERN
ERN-EYE
ERN-Skin
EpiCARE
BOND ERN
ERKNet
VASCERN
ERN GENTURIS
TRANSPLANT-CHILD
ERNICA
RITA
ERN-LUNG
ReCONNET
ERN-RND
RARE-LIVER
EURACAN
PaedCan-ERN
MetabERN
EuroBloodNet
ITHACA
EUROGEN
GUARD-HEART
EURO-NMD



# The Intersectoral Global Action Plan **on epilepsy** and other neurological disorders (2022-2031)

## 5 STRATEGIC OBJECTIVES

World Health Organization

1. To raise the prioritization and strengthen governance
2. To provide effective, timely and responsive diagnosis, treatment and care
3. To implement strategies for promotion and prevention
4. To foster research and innovation and strengthen information systems
5. To strengthen the public health approach to epilepsy

Development and integration of neurological disorders in comprehensive, multisectoral policies and plans, based on evidence and social



# STRATEGIC OBJECTIVES

## 1 To raise the prioritization and strengthen governance

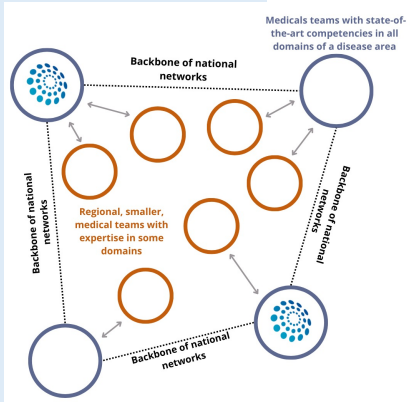
- ✓ **Significant discrepancies and inequalities between health care systems even within the European Union.**
- ✓ **Need to** developpe and integrate neurological disorders in comprehensive, multisectoral policies and plans, based on evidence and social.

| Global target(s) | Key indicator(s) |
|---|---|
| **Global target 1.1:** **75% of countries will have adapted or updated existing national policies, strategies, plans or frameworks to include neurological disorders by 2031** | Existence of an operational national policy, strategy, plan or framework that has been adapted or updated to include neurological disorders. |
| **Global target 1.2:** **100% of countries will have at least one functioning awareness campaign or advocacy programme for neurological disorders by 2031** | Existence of at least one functioning awareness campaign or advocacy programme for neurological disorders. |

# STRATEGIC OBJECTIVES

## 2 To provide effective, timely and responsive diagnosis, treatment and care

- ✓ Most of the neurological diseases, in neonates, children, adults and elderly **first manifest with non-specific symptoms**.
- ✓ They can be considered as “rare”, or “complex” only once diagnosed.




- ✓ This is the reason why the ERNs must become the backbone of national Heath Care Systems.

| Global target(s) | Key indicator(s) |
|---|---|
| **Global target 2.1:** **75% of countries will have included neurological disorders within universal health coverage benefits package by 2031** | Existence of a set of evidence informed, prioritized, essential, quality health services and supports for neurological disorders within the universal health coverage benefits package. |
| **Global target 2.2:** **80% of countries will provide the essential medicines and basic technologies required to manage neurological disorders in primary care by 2031** | Countries report availability of essential medicines and basic technologies to manage neurological disorders in primary care. |

# STRATEGIC OBJECTIVES

## 3 To implement strategies for promotion and prevention

- ✓ The first prenatal diagnostic screening was developed in 2000 and the first results of the 1000 genomes project published in 2010:

what justifies such huge delays in establishing a systematic newborn screening, while endlessly praising the importance of early diagnosis .

| Global target(s) | Key indicator(s) |
|---|---|
| **Global target 3.1:** **80% of countries will have at least one functioning intersectoral programme for brain health promotion and the prevention of neurological disorders across the life course by 2031** | Existence of at least one functioning intersectoral programme for brain health promotion and the prevention of neurological disorders across the life course. |
| **Global target 3.2:** **The global targets relevant for prevention of neurological disorders are achieved as defined in:**<br>• **the Global action plan for prevention and control of noncommunicable diseases 2013-2020**<br>• **Defeating meningitis by 2030: a global road map,**<br>• **Every newborn: an action plan to end preventable deaths** | Relevant indicators as defined in:<br>- the Global action plan for prevention and control of noncommunicable diseases 2013-2020;<br>- - Defeating meningitis by 2030: a global road map,<br>- - Every newborn: an action plan to end preventable deaths. |

# STRATEGIC OBJECTIVES

## 4 To foster research and innovation and strengthen information systems

- ✓ The 24 ERNs are funded to coordinate the development of REGISTRIES across the EU HCPs. It is the role of the Member States and the HCP administrations to facilitate their development.
- ✓ Fostering research is one of the main missions of the 24 ERNs.

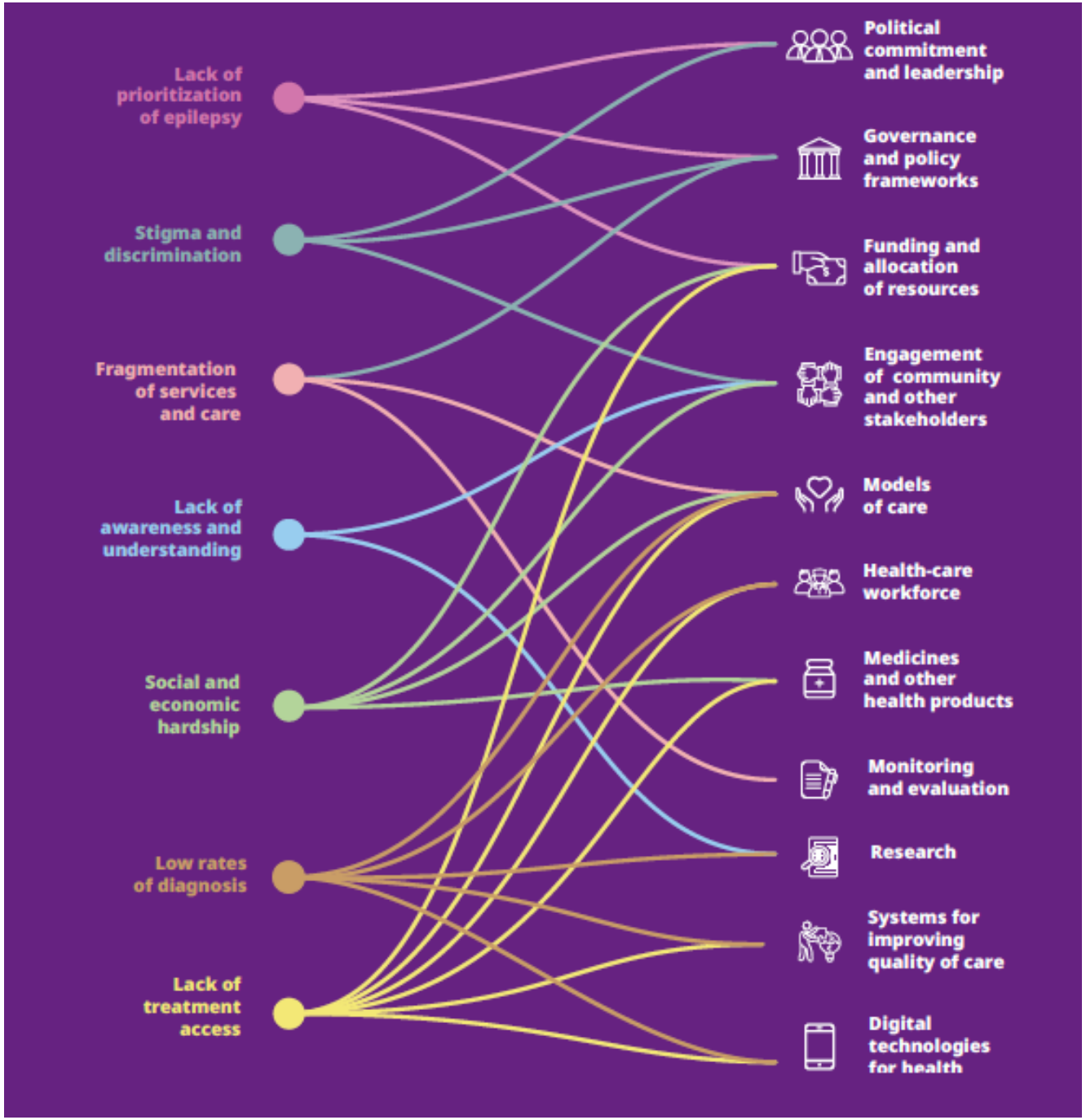
| Global target(s) | Key indicator(s) |
|---|---|
| **Global target 4.1:** **80% of countries routinely collect and report on a core set of indicators for neurological disorders through their national health data and information systems at least every three years by 2031.** | Countries have functioning health data and information systems to routinely collect and report on a core set of indicators for neurological disorders |
| **Global target 4.2:** **The output of global research on neurological disorders doubles by 2031.** | Number of published articles on neurological disorders research (defined as research articles published in an indexed and peer-reviewed journal). The indicator measures the output of neurological disorders research as defined by national published research studies. |

# STRATEGIC OBJECTIVES

## 5 To strengthen the public health approach to epilepsy


| Global target(s) | Key indicator(s) |
|---|---|
| **Global target 5.1:** **By 2031, countries will have increased service coverage for epilepsy by 50% from the current coverage in 2021.** | Proportion of persons with epilepsy who are using services over the past 12 months (%). |
| **Global target 5.2:** **80% of countries will have developed or updated their legislation with a view to promote and protect the human rights of people with epilepsy by 2031.** | Existence of national legislations relevant to epilepsy that are in line with international and regional human rights instruments. |

# Levers for change




**The levers and related actions are not independent but are interconnected. All are essential to an integrated national response to epilepsy**

# Models of care

A model of care is a conceptualization of **how services should be delivered, including the processes of care**, organization of providers, management of services and identified roles and responsibilities of different platforms and providers.

Models of care should be attentive to the different needs of **subgroups of people with epilepsy** and their conceptualization should include the perspectives of people with epilepsy.

Models of care should be defined in different sectors and across different services and should include **management of co-morbid conditions, self-care and telehealth services**.

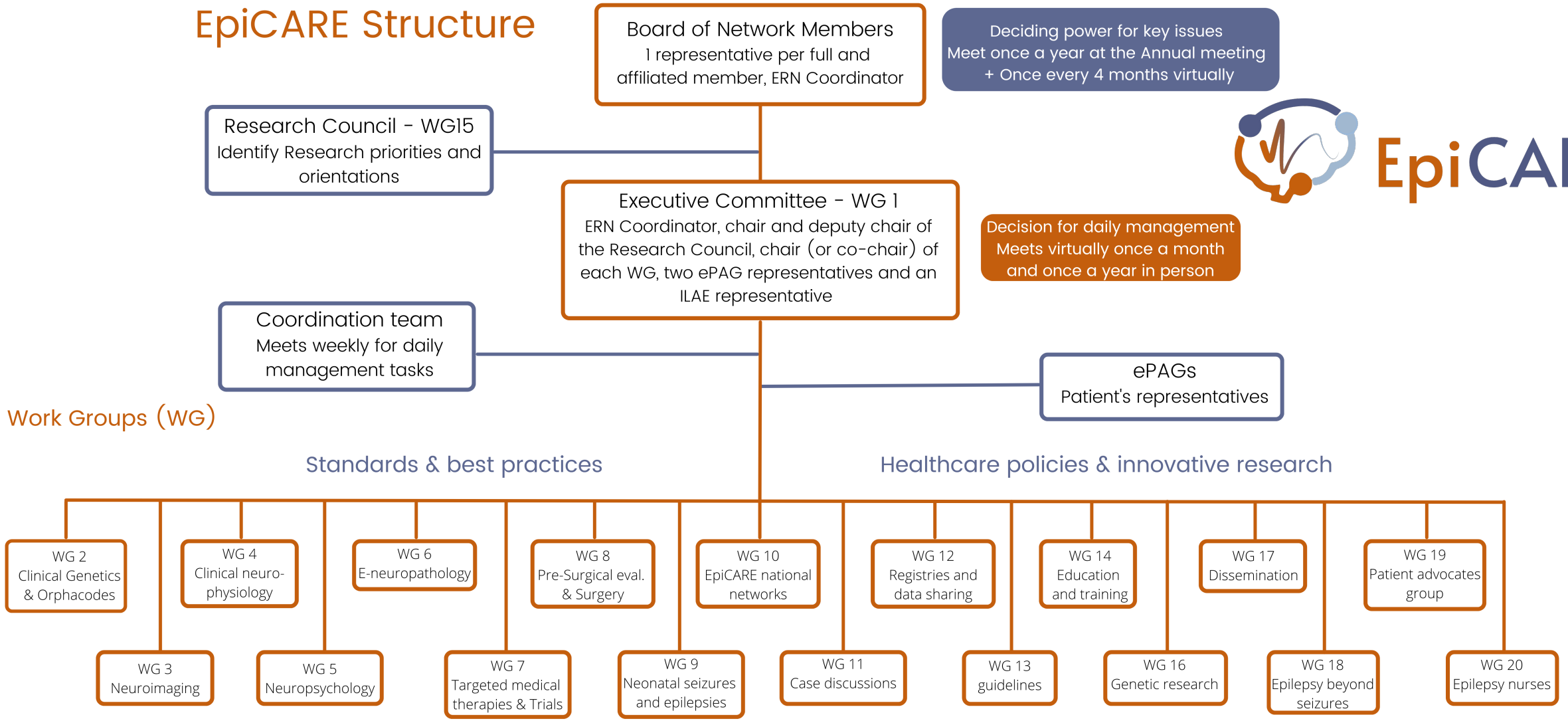
# Models of care

Review existing models of care and the connections between them both vertically (e.g., at different levels of the health system) and horizontally (e.g., between sectors), with the goal of updating them according to the best evidence available.

Develop evidence-based models of care which include referral and back-referral and clear routes to access to services beyond primary care.

Analyse the **cost-effectiveness of models of care** and ensure regional sharing of best practices and innovative approaches.

# A complex structure adapted to the specificities & complexity of epilepsy care



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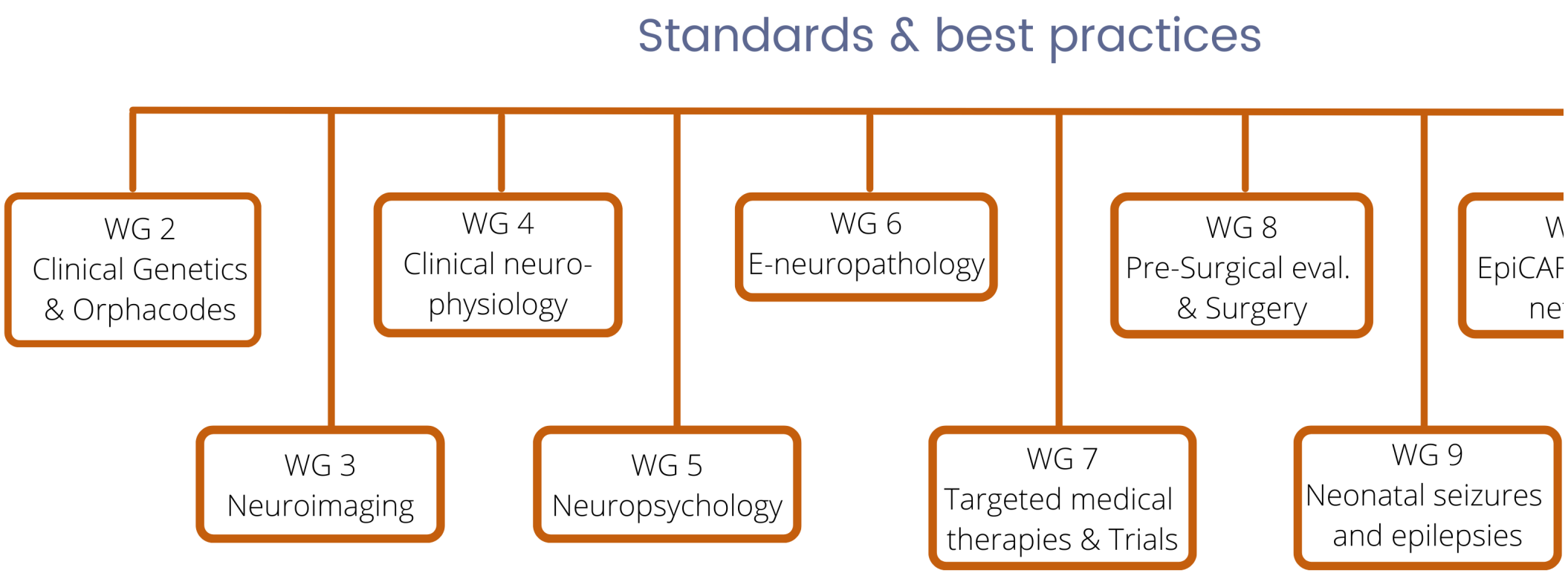
EpiCARE



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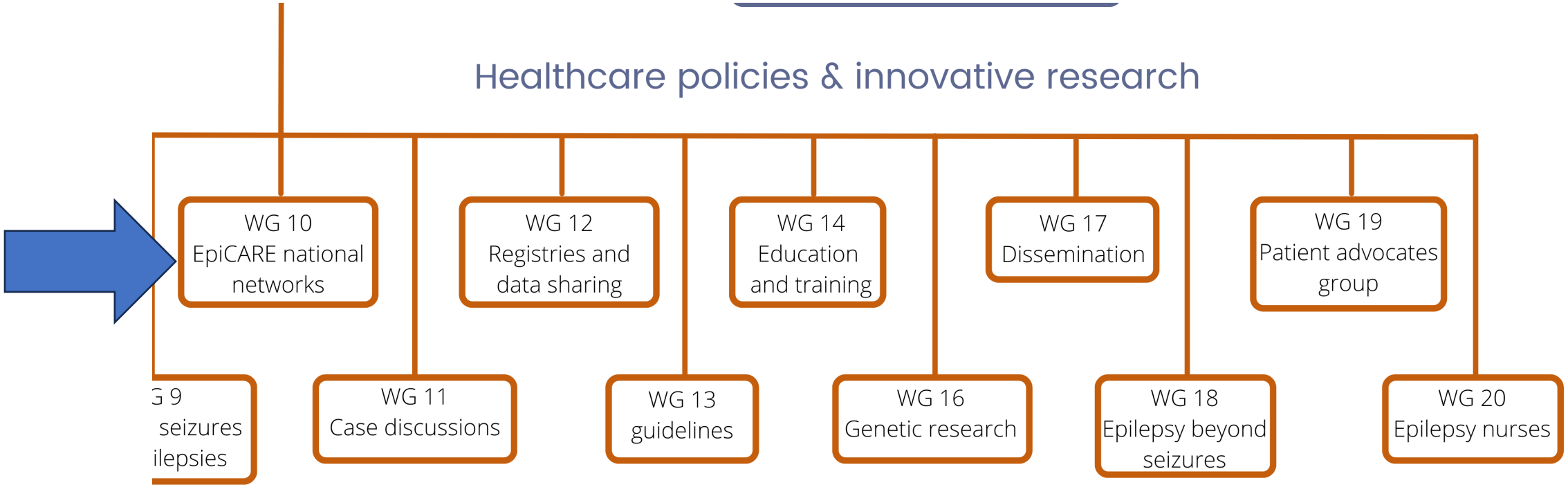

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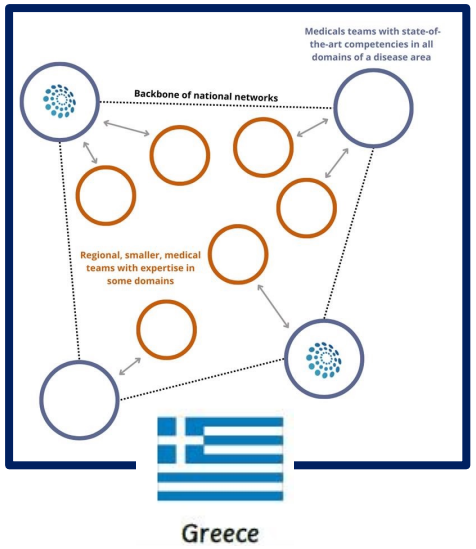
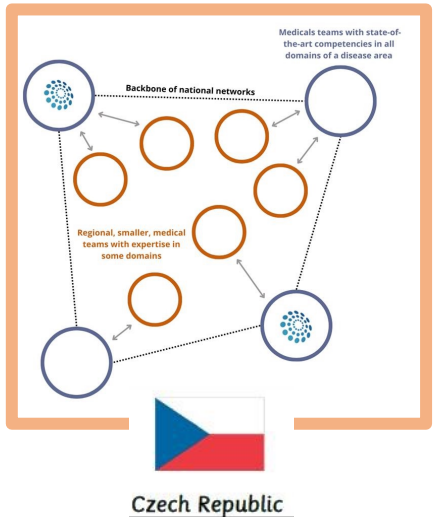
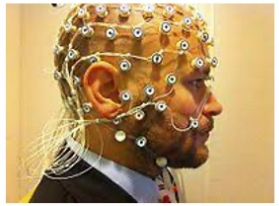


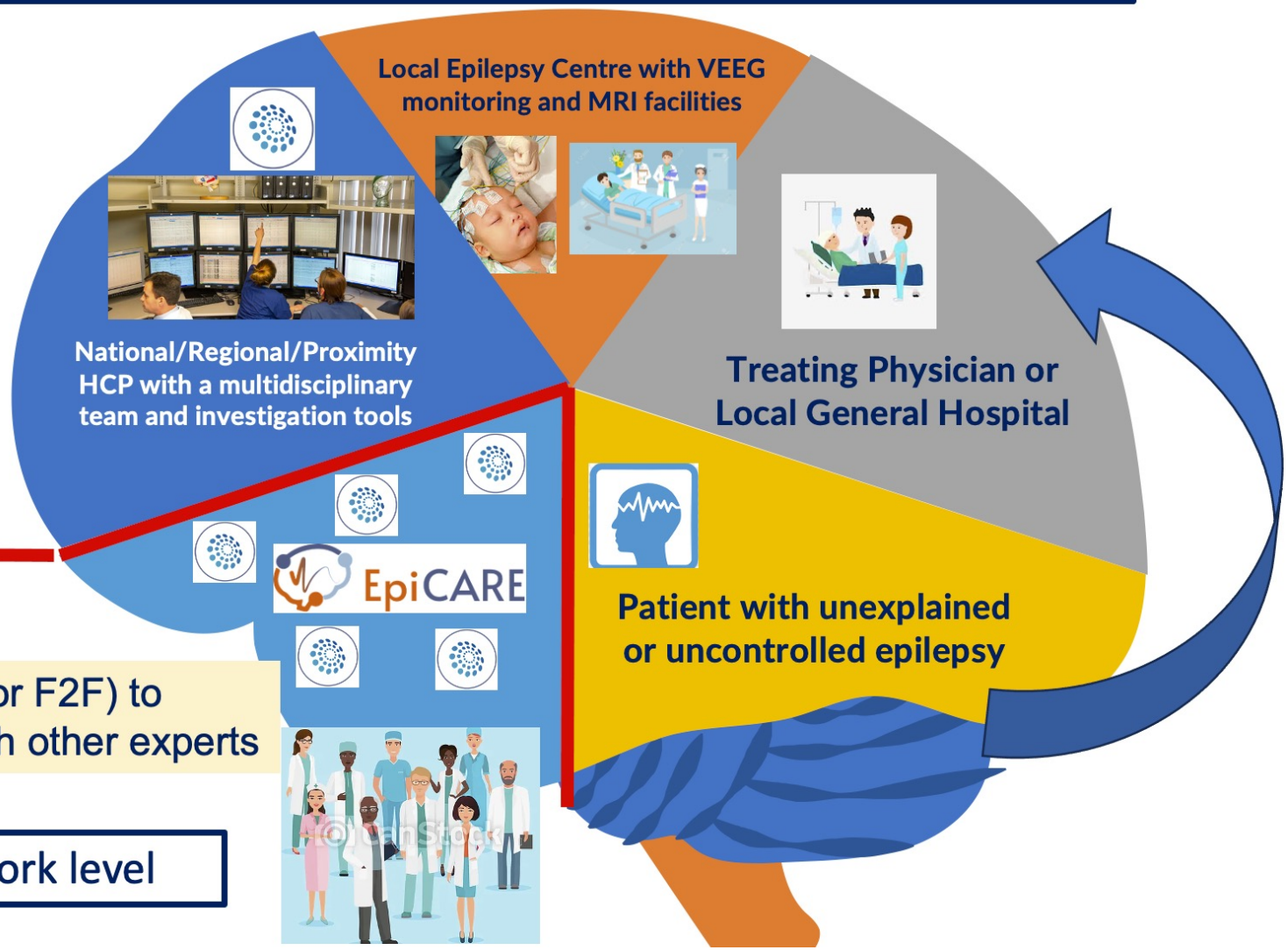

Greece




Czech Republic

National/Regional/Proximity level





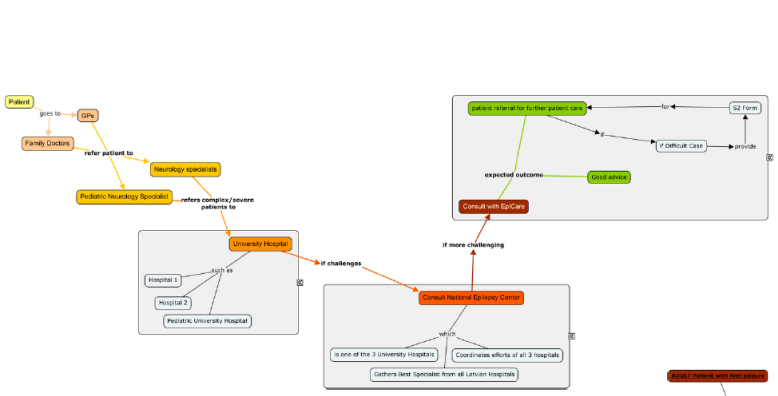

ERN (CPMS and/or F2F) to share opinions with other experts

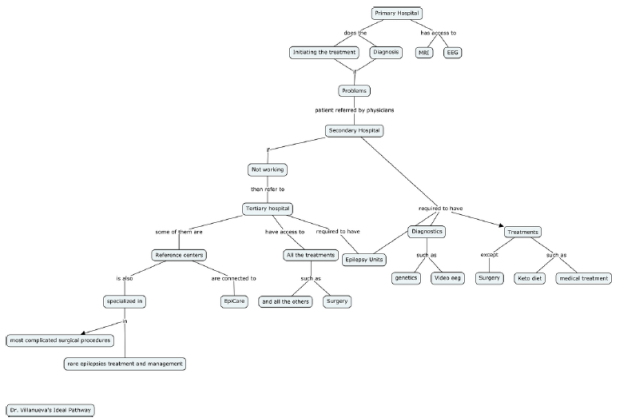
EpiCARE Network level

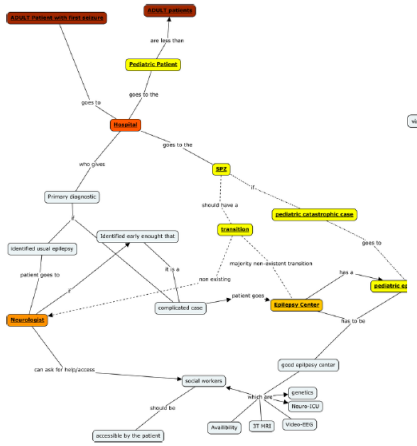
# “The quest for diagnosis often remains an odyssey”

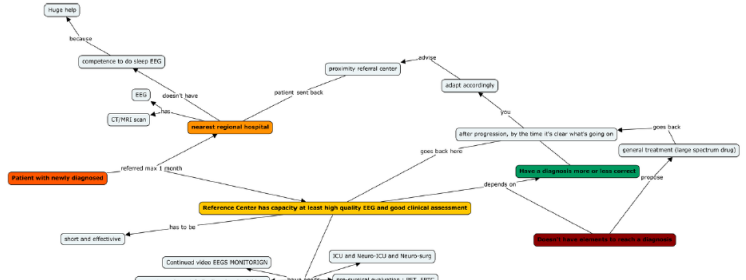
## Health care pathways in epilepsy are far from being comparable within Europe

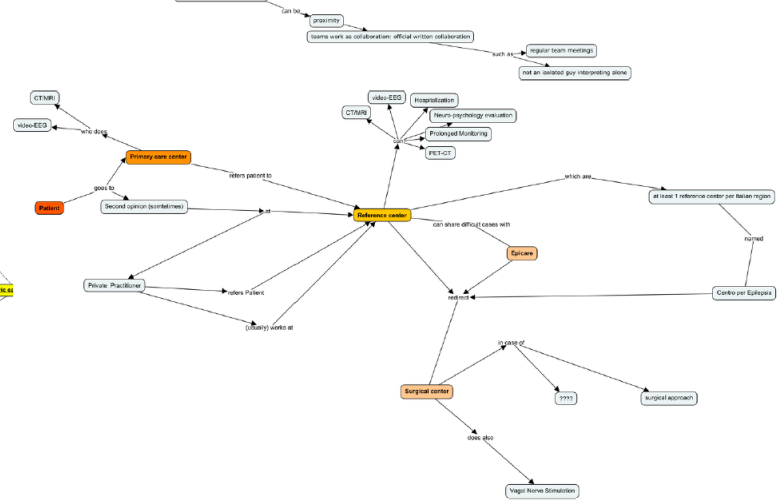




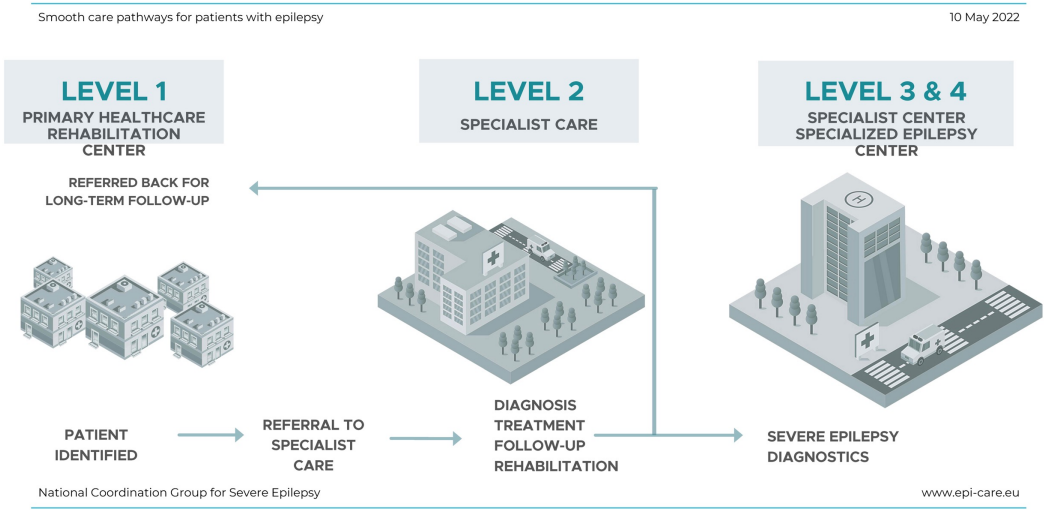



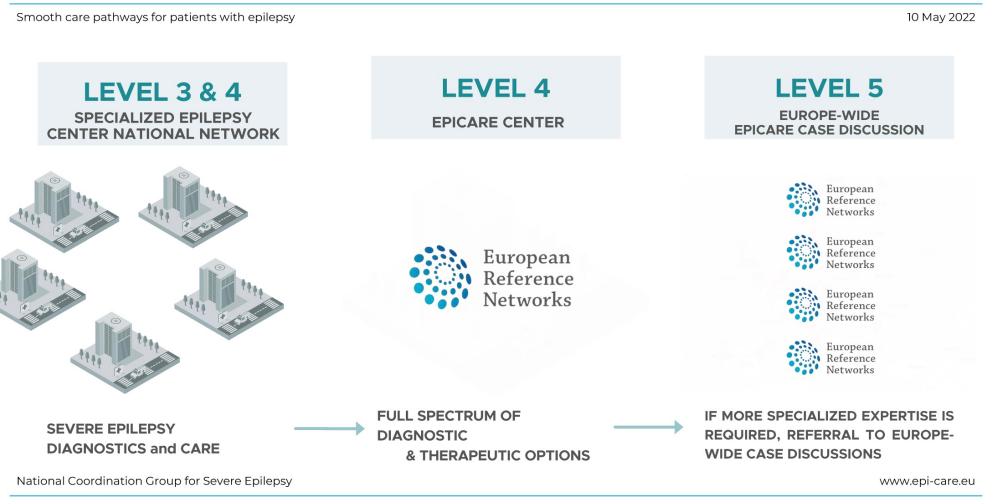




# “The quest for diagnosis often remains an odyssey”

What data do we have that supports the suggested pathway:

- Early access to a valid diagnosis (when knowledge is available)
- Early access to optimal screening (when the Dg hypothesis …)
- Early access to state-of-the-art treatment strategies
- Candidates to pre-surgical evaluation and outcomes



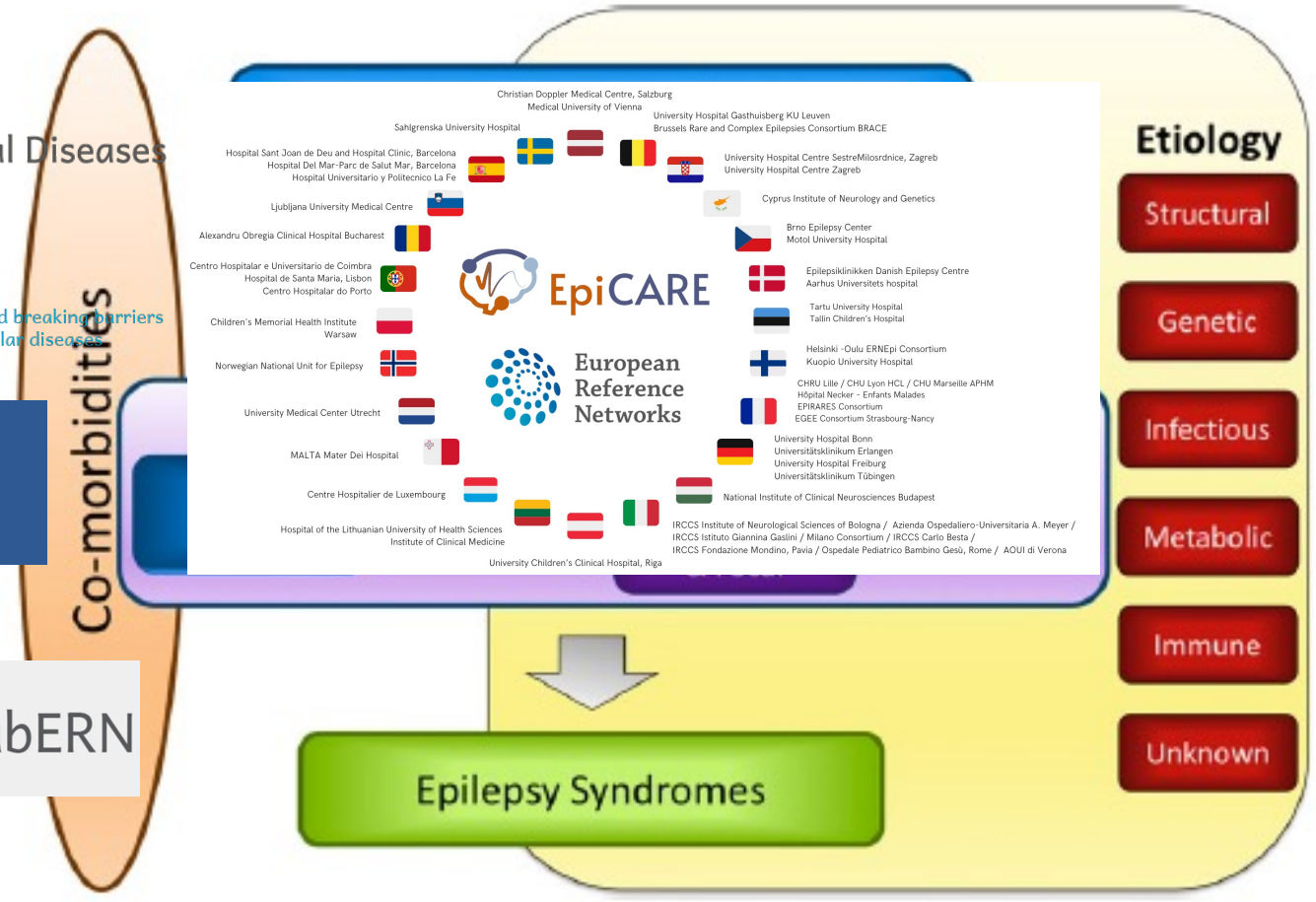

# Aetiologies and/or co-morbidities ?

European Reference Network | Neurological Diseases (ERN-RND)

EURO-NMD | Building bridges and breaking barriers in rare neuromuscular diseases

ITHACA

European Reference Network | MetabERN

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ITHACA

European Reference Network | MetabERN

# ERN EURO-NMD

**Teresinha Evangelista, MD**

**Pitié-Salpetrière Hospital, AP-HP**

**Paris**

With the support of the Association of the Institute of Myology (AIM)

# Members

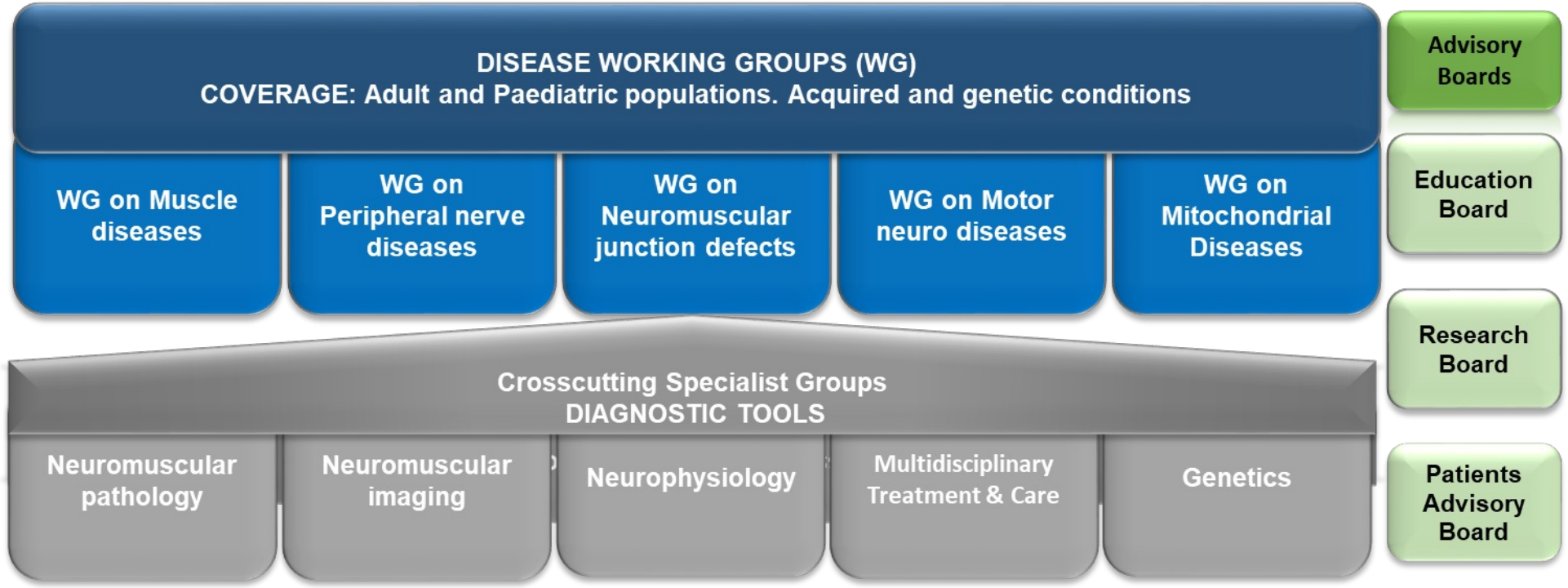
- **Thematic Area:** Rare neuromuscular diseases

- **2017:** 61 expert centres from 14 Member States (Brexit – 4)
- **2022:** 84 expert centres from 25 Member States
  - 76 HCPs Full Members
  - 6 Associated National Centres
  - 2 National Coordination Hubs
- **2024:** **74 HCPs Full Members (Total of 82 HCPs)**

# General Objectives

- Improve the quality and equity of healthcare for patients with NMD
- Enable the exchange of knowledge through teaching and training
- Facilitate translational research

# Working Areas



# EURO-NMD 23-27
# Consortium

Hôpital Pitié-Salpêtrière AP-HP

**WP1 (Coordination), WP2 (Dissemination)**
**WP3 (Evaluation)**
**WP6** (Training and Education)
**WP8** (Capacity Building (Ukrainian) )
**WP9** (Research promotion and needs)

UNIVERSITÄTS KLINIKUM FREIBURG

**WP5** - Registries, data management and analysis

Radboudumc university medical center

SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara

**WP4** - Healthcare and CPMS

AZIENDA OSPEDALIERO UNIVERSITARIA PISANA

**WP7 -** Clinical Practice Guidelines and Clinical Decision Support Tools



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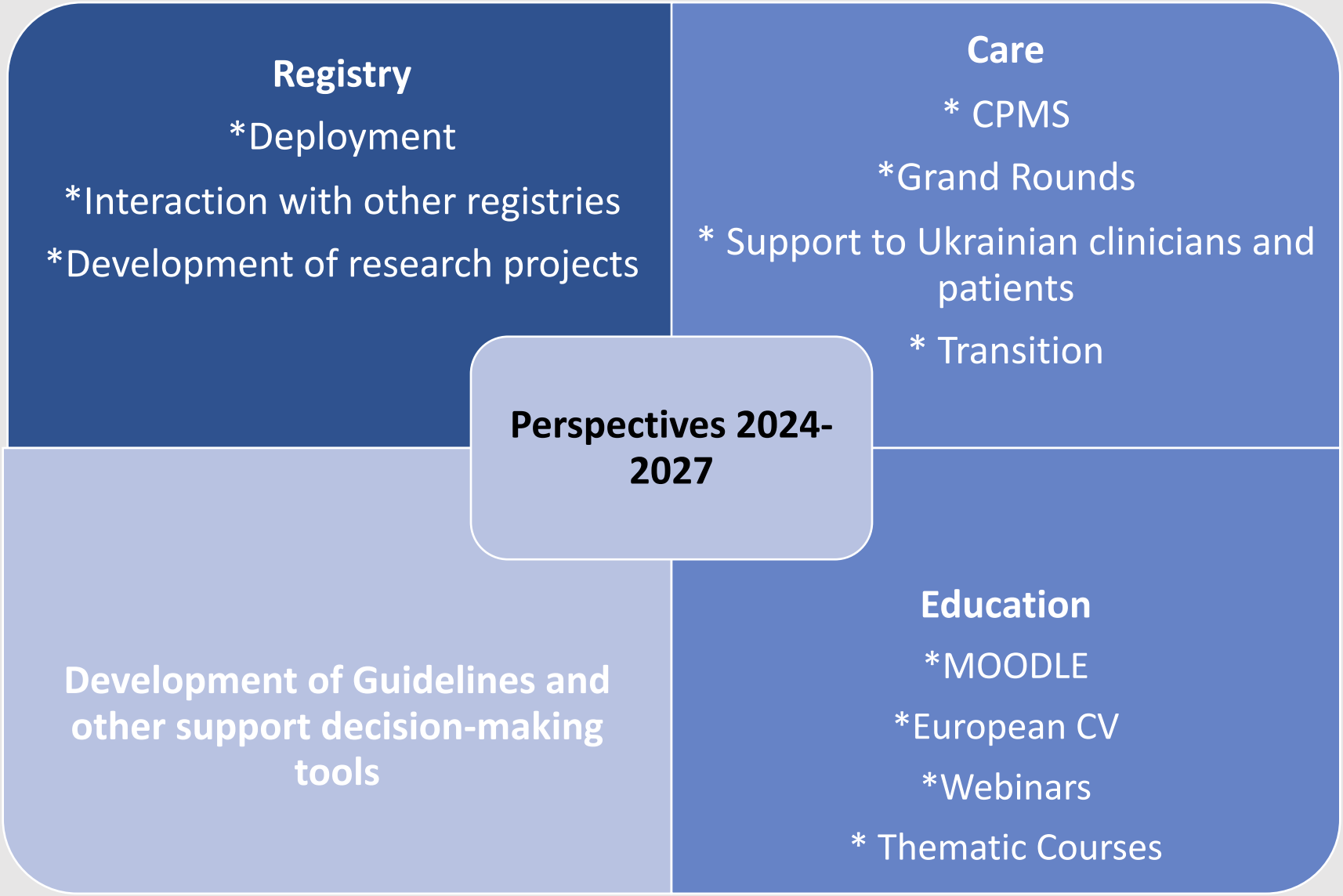

Registry
*Deployment
*Interaction with other registries
*Development of research projects
Care
* CPMS
*Grand Rounds
* Support to Ukrainian clinicians and patients
* Transition
Perspectives 2024-2027
Development of Guidelines and other support decision-making tools
Education
*MOODLE
*European CV
*Webinars
* Thematic Courses

# Education WP6

Hôpital Pitié-Salpêtrière AP-HP

Education advisory Board
Working Group leaders

WP 7

AZIENDA OSPEDALIERO UNIVERSITARIA PISANA

European Reference Network for rare or low prevalence complex diseases — Network Neuromuscular Diseases (ERN EURO-NMD)

European Reference Networks for rare or low prevalence complex diseases — Network Neurological Diseases (ERN-RND)

EpiCARE

European Reference Network for rare or low prevalence complex diseases — Network Epilepsies (ERN EpiCARE)

European Reference Network for rare or low prevalence complex diseases — Network Hereditary Metabolic Disorders (MetabERN)

European Reference Network for rare or low prevalence complex diseases — Network Eye Diseases (ERN-EYE)

ean the home of neurology

EUROPEAN PAEDIATRIC NEUROLOGY SOCIETY

## Specific Objective

| | |
|---|---|
| WP6 | Development of Education and Training activities targeting healthcare professionals and patients |

# Workshops/ summer schools

Ongoing:

EURO-NMD translational Summer School (5th Edition in 2023) : 6th edition under preparation (**EACCME®** credits)

Neuropathies Rehabilitation Summer School: Rome September 18-21, 2023 (**EACCME®** credits) √

Plan for training on Multidisciplinary care 2024

# MOODLE – EURO-NMD Academy

- Moodle-based LMS platform
- We are in **an experimental phase** of the platform
- Courses will be **release in a progressive manner**

- The courses will be aimed at **medical, nursing and other healthcare professions**
- A course satisfaction form will also be included at its conclusion
- There will be a gradual process of accreditation of the courses

# Podcasts in Ukrainian

- Adaptation of some webinars to become podcasts from the Ukrainian community

- With translation by a native language speaker

**Thank you to:**
Oksana POGORYELOVA
Webinars coordinator
Speakers of different webinars

# Facilitate research

- Dissemination of information about Research grants/opportunities (newsletter, meetings, website)
- **ERN Registry**
- Increase involvement of HCPs in the **ongo**
- Collaboration with the EMA /
- Support suggestions from the HCPs/E… jects

**The ERN is a privileged tool to establish international networks and to facilitate additional funding**

SolveRD
Solving the Unsolved Rare Diseases

SCREEN 4CARE

ERICA

Integrating the ERNs into the EU's health systems: joint action under the EU4HEALTH health programme ("JARDIN")

# Inter ERNs Working Groups (RND; EPICARE; EURO-NMD)

## Lead by EURO-NMD

- Mitochondrial diseases
- Gene therapy
- NGS

- Insufficient funding
- Not enough personnel
- Monitoring and Evaluations

**Hospital**
**NHS**
**EC**

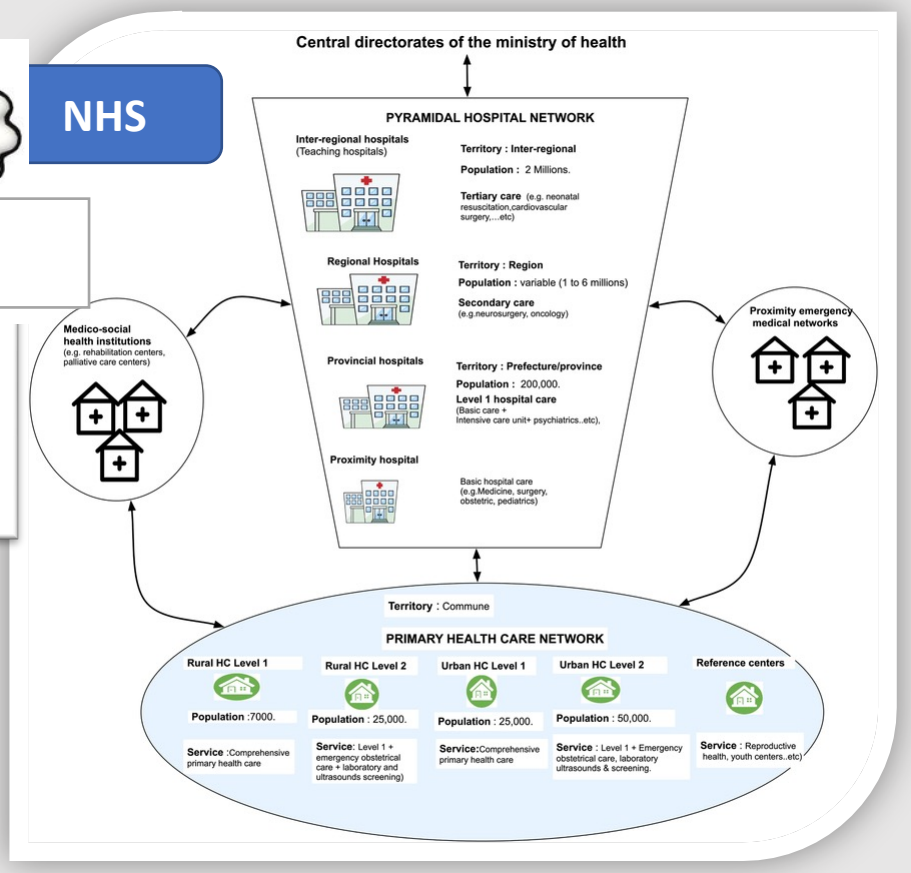
Navigation between different instances is not always easy

NHS

Lack of integration in the NHS

European Reference Network
for rare or low prevalence complex diseases

Lack of funding for the HCPs




Lack of engagement of certain HCPs

- Legal context (CPMS; Registry)



- Multiple Grants: Work load

Multiple contracts and specific constrains to be able to develop the projects

Rules that change



**https://ern-euro-nmd.eu/**

**Contact us**

**info@ern-euro-nmd.eu**

**Sign up to our Newsletter**

go to @euro_nmd Twitter

go to EURO-NMD YouTube Channel

# EpiCare - ITHACA transERN cooperation

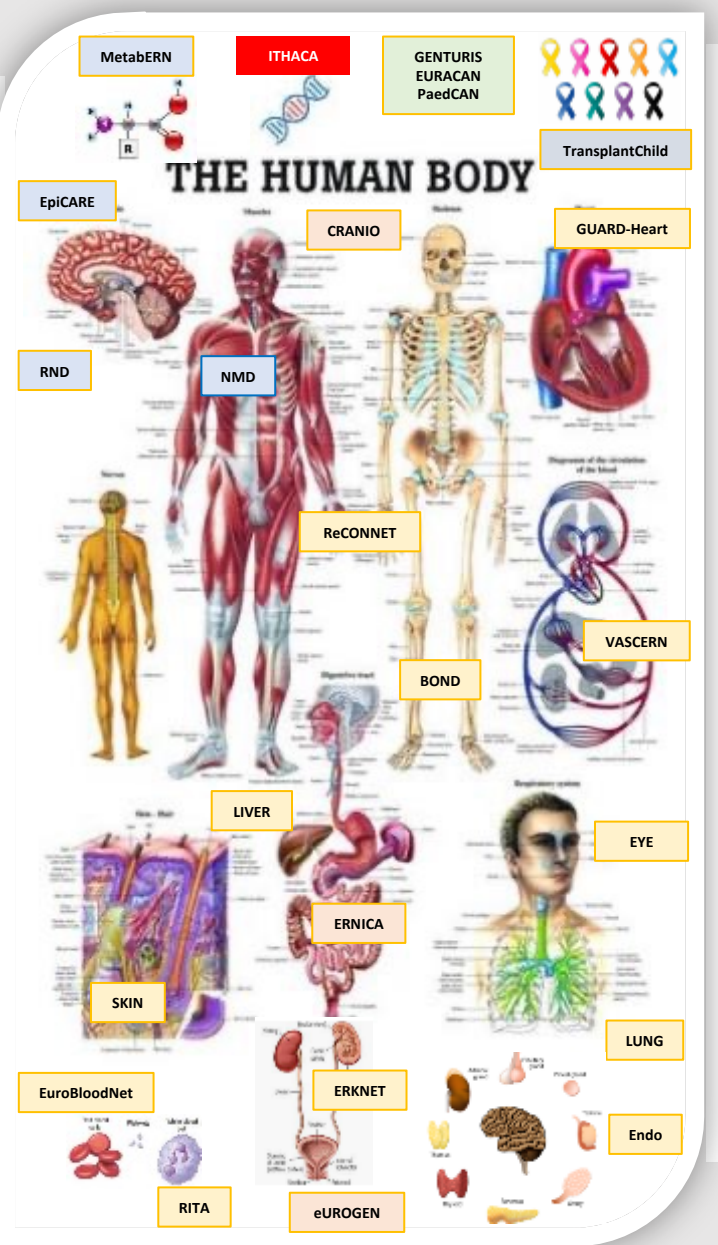
Alain Verloes



Co-funded by the European Union

# 24 ERNs covering all aspects of rare/complex human diseases + rare cancers

- Organs/systems (12)
  - Gateway to Uncommon And Rare Diseases of the HEART - GUARD-HEART
  - ERN on Respiratory Diseases - ERN-LUNG
  - ERN on Rare Hepatological Diseases - RARE-LIVER
  - European Rare Kidney Diseases RN – ERKNet
  - ERN on Rare Multisystemic Vascular Diseases – VASCERN
  - Rare Endocrine Conditions - Endo-ERN
  - Rare Bone Disorders - ERN BOND
  - ERN on Rare and Undiagnosed Skin Disorders - ERN-Skin
  - ERN on Rare Hematological Diseases - EuroBloodNet
  - ERN on Rare Eye Diseases - ERN-EYE
  - Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases Network - RITA
  - Rare Connective Tissue and Musculoskeletal Diseases Network – ReCONNET
- Developmental anomalies/Genetics (1)
  - ERN on Developmental and Neurodevelopmental Anomalies - ITHACA




- Neurology (4)
  - ERN on Rare and Complex Epilepsies - EpiCARE
  - ERN on Rare Neurological Diseases - ERN-RND
  - ERN for Rare Neuromuscular Diseases - EURO-NMD
  - ERN for Rare Hereditary Metabolic Disorders – MetabERN
- Surgery/mixed (4)
  - Rare craniofacial anomalies and ENT disorders - ERN CRANIO
  - ERN on Rare inherited and congenital anomalies - ERNICA
  - Rare Urogenital Diseases – eUROGEN
  - ERN on Transplantation in Children – TransplantChild
- Oncology (3)
  - ERN on GENetic TUmour RIsk Syndromes - ERN GENTURIS
  - ERN on Rare Adult Cancers (solid tumors) - EURACAN
  - ERN for Paediatric Cancer (haemato-oncology) - PaedCan-ERN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Intellectual disability, TeleHealth, Autism and Congenital Anomalies

# https://ern-ithaca.eu

- La
  - 71 from 25+1 countries,
  - Most HCP are Genetic Depts in teaching hospitals


- Scope
  - Developmental anomalies
    - Single malformations and MCA
    - **NDD (ID, ASD)**
  - Genetic, multifactorial (e.a. spina bifida) or environmental



Co-funded by the European Union

# Work Groups and Task Forces for NDD

- Focus
  - ID (monogenic, genomic, environmental/polygenic)
  - ASD
  - PIMD - Profound intellectual and multiple disabilities
  - Psychiatric expression of genetic disorders (NEW)
  - Fetal pathology
  - Spina bifida (transERN collaboration with eUROGEN)
    - Postnatal
    - Fetal surgery of dysraphisms

- 15 thematic working groups (> 40 Task forces)
  - NDD WG
  - Research WG
  - Teaching & training WG
  - Guidelines WG
  - Register WG…

- Multibeneficiary
  - Amsterdam, Rotterdam, Groningen, Rome OPBG (Bern)
  - 10 project mangers



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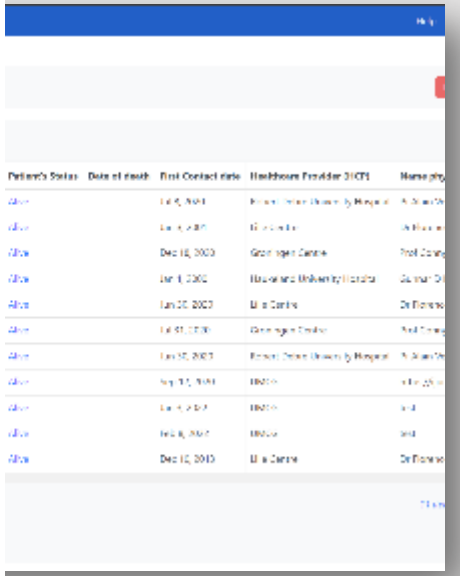
# CPG

- Clinical Practice Guidelines (CPG) and Clinical Decision Supporting Tools (CDST)
  - Using **PICO** questions as framework to help formulate clinical research questions
    - P: Patient, Population, or Problem ; I: Interventions ; C: Comparison of intervention; O: Outcome to measure, improve, or affect
  - Based on a combination of
    - **AGREE II** : tool for evaluation of the quality of CPG ("Appraisal of Guidelines for Research and Evaluation")
    - **DELPHI** : methodology to build final consensus among experts by iterated rounds on PICO
    - Multiple e-meetings and final F2F consensus meeting
  - + Lay versions in several languages
- Achievements
  - Syndrome-specific: valproate, Beckwith-Wiedemann, C de Lange, Phelan-McDermid, Rubinstein-Taybi
- In development
  - *Syndrome-specific*: Noonan, Kabuki, Williams, Fragile X, Kleefstra, spina bifida
  - *Transversal*: challenging behavior, transition of care, sleep disorders , general care of adults with ID, PIMD/poly-handicap (child and adult)…
- SYNERGY: official participation on Epilepsy aspects of currently developped/foreseen CPGs
- Transversal CPG: epilepsy in severly handicapped children / in adults with ID

# ILIAD register

- A simple EU-wide register of patients with monogenic ID ± ASD
  - Mixed federative architecture : reduce GDRP-based regulatory burden
  - Each HCP may harbour a clone of the database structure
  - Federated queries possible
  - Development : MOLGENIS (Groningen UMC)
- Scalable data repository
  - Pseudo-anomymized records (SPIDER)
  - Minimal dataset + Genetic definition (SNVs and/or CNVs)
  - Extended subregistries « on demand »
    - Requires specifi Task Force for curation
    - Currently developing : RASopathies, PMD, Genida
    - **Possible synergies with syndromic epilepsy/ID genes**
  - Open to biobanks, patient-supported registries…
- Many potential overlaps → links
  - Brain malformation (micro, migration, CC…): to explore
  - ID + epilepsy genes subregistries

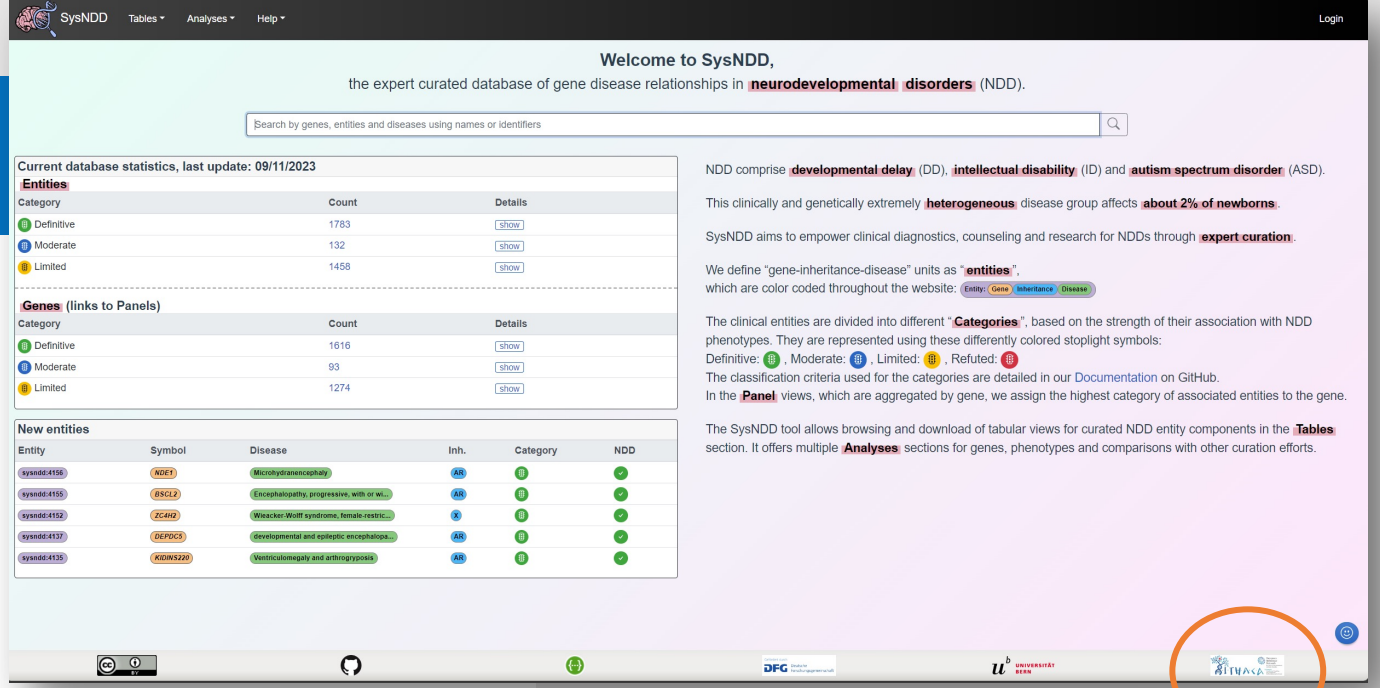
ILIAD beta version

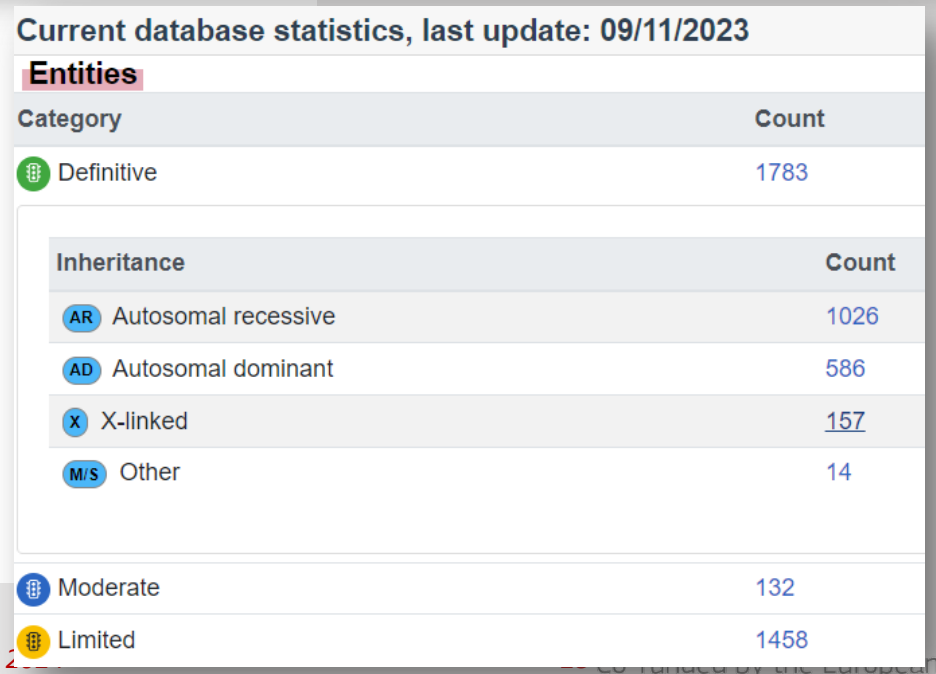



Co-funded by the European Union

# SysN

- A curated database of ID genes
- Supported by Pr Christiane ZWEIER (Bern Univ)
- ITHACA support
  - Curation
- Integration/connexion with Orphanet



# T & T

- Webinars
  - Multiple topics, professional & lay-oriented
  - TEAMS support
  - Eur Soc Ped Neurology as Affiliated Partner
  - **Let's have some shared webinars !!!**

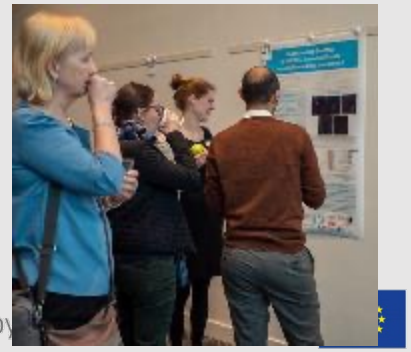

- APOGeE
  - Online e-handbook on medical genetics
  - Adopted as reference for ECCMG certificate (UEMS)
  - With strong accent on NDD and developmental anomalies
  - In development (beta version)
  - **We would love to have help for some chapters and vignettes**
  - Achievement T2, 2024
- Others: 2 MOOCs

# T & T: EuroDysmorpho 34

- EuroDysmorpho
  - A 3-day workshop dedicated to developmental anomalies + educational talks
  - Oriented to young Geneticists and Young child Neurologists
  - 120 participants
    - 2023: Lisbon
    - 2024: Ljubliana
    - 2025: Vilnius


- EuroNDD

# T & T : 2d E

- Objective: crossed vision across specialties on **ID, ASD, child psychosis**
  - Mixing in a unique event Neuroscience, Genetics, Social Sciences and Medicine interested by ID, ASD, and other NDDs
  - Promote networking across EU, Incubate projects, researchs…
  - Invited speakers, oral presentation & posters
  - EuroNDD 2023 : 240 participants (free meeting, catering supported by ITHACA)
  - Organisation : Prof. Tjitske Kleefstra (Rotterdam), Prof. Christiane Zweier (Bern)
- EuroNDD 3: Warshaw 2025
- **EpiCare involved in the organisation in 2024**


ITHACA

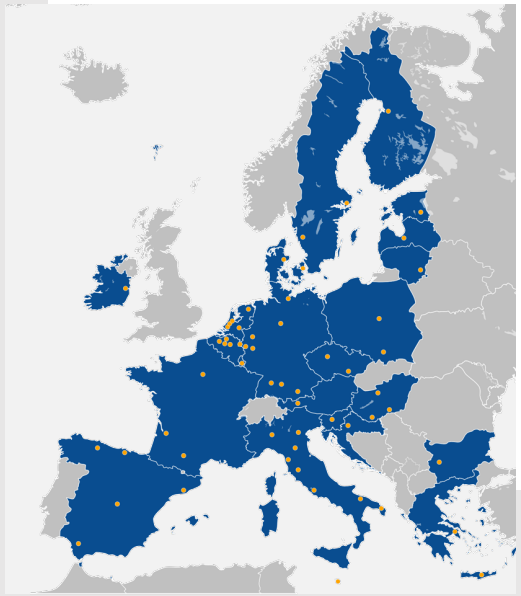
# European Reference Network for Rare Neurological Diseases, ERN-RND



Co-funded by the European Union

# ERN-RND – European Reference Network for rare neurological diseases

- 68 expert centres in 24 EU countries
- > 35.000 patients per year (adults and paediatric)



| Country | N members |
|---|---|
| Austria | 1 |
| Belgium | 4 |
| Bulgaria | 1 |
| Croatia | 1 |
| Cyprus | 1 |
| Czech Republic | 4 |
| Denmark | 2 |
| Finland | 1 |
| France | 6 |
| Germany | 9 |

| Country | N members |
|---|---|
| Greece | 1 |
| Hungary | 3 |
| Ireland | 1 |
| Italy | 9 |
| Lithuania | 1 |
| Netherlands | 6 |
| Poland | 2 |
| Slovenia | 1 |
| Spain | 8 |
| Sweden | 2 |

| Country | N members |
|---|---|
| Estonia | 1 |
| Latvia | 1 |
| Luxembourg | 1 |
| Malta | 1 |

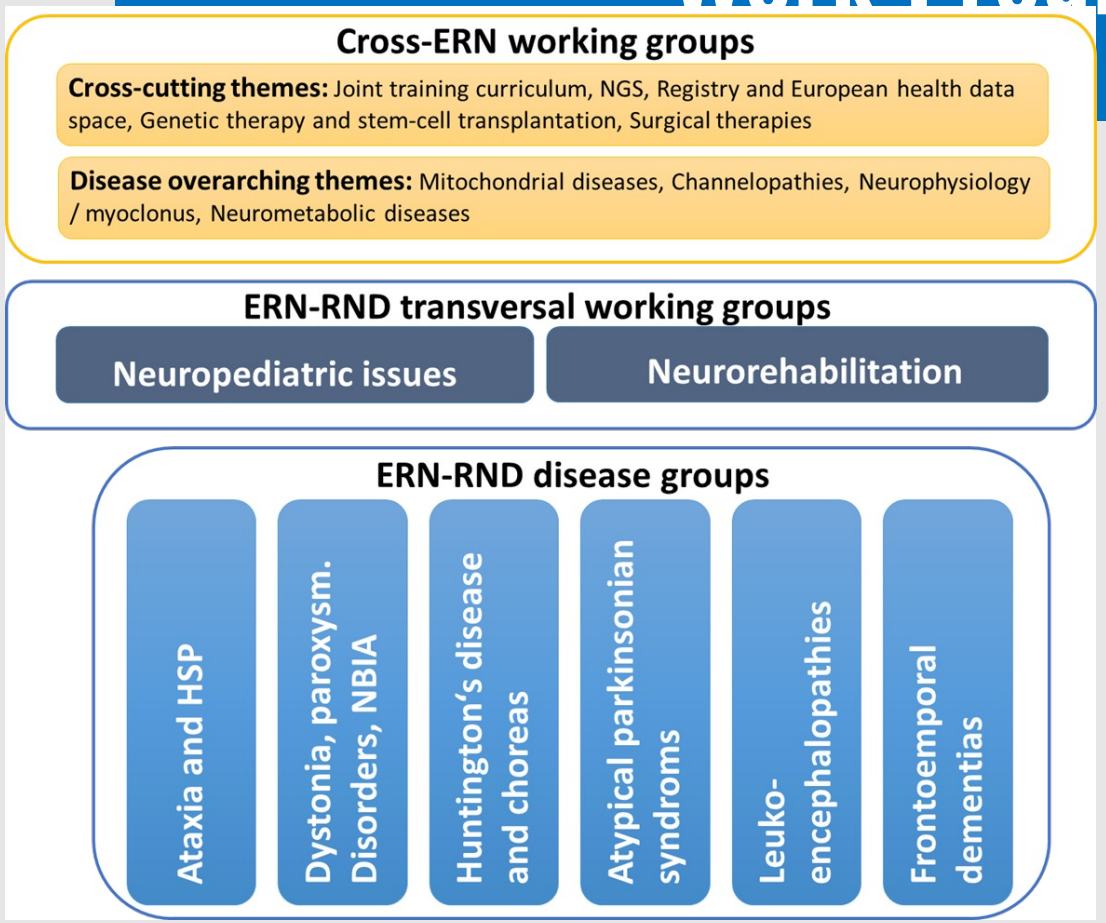
## Diseases covered

- Ataxia and HSP
- HD and Choreas
- Dystonia, paroxysmal disorders and NBIA
- Leukoencephalopathies
- Atypical parkinsonian syndromes
- Frontotemporal dementia

## Highly specialised healthcare services

- Next Generation Sequencing
- Neuroimaging
- Deep brain stimulation
- Stem Cell transplantation
- Etc.

# Work Program 2023 - 2027




- Work Package 1. Coordination
- Work Package 2. Dissemination
- Work Package 3. Evaluation
- Work Package 4. Healthcare and CPMS
- Work Package 5. Registries, data management and analysis
- Work Package 6. Training and education
- Work Package 7. Clinical Practice Guidelines and Clinical Decision Support Tools

# Added value of ERNs for people living with RD and member states

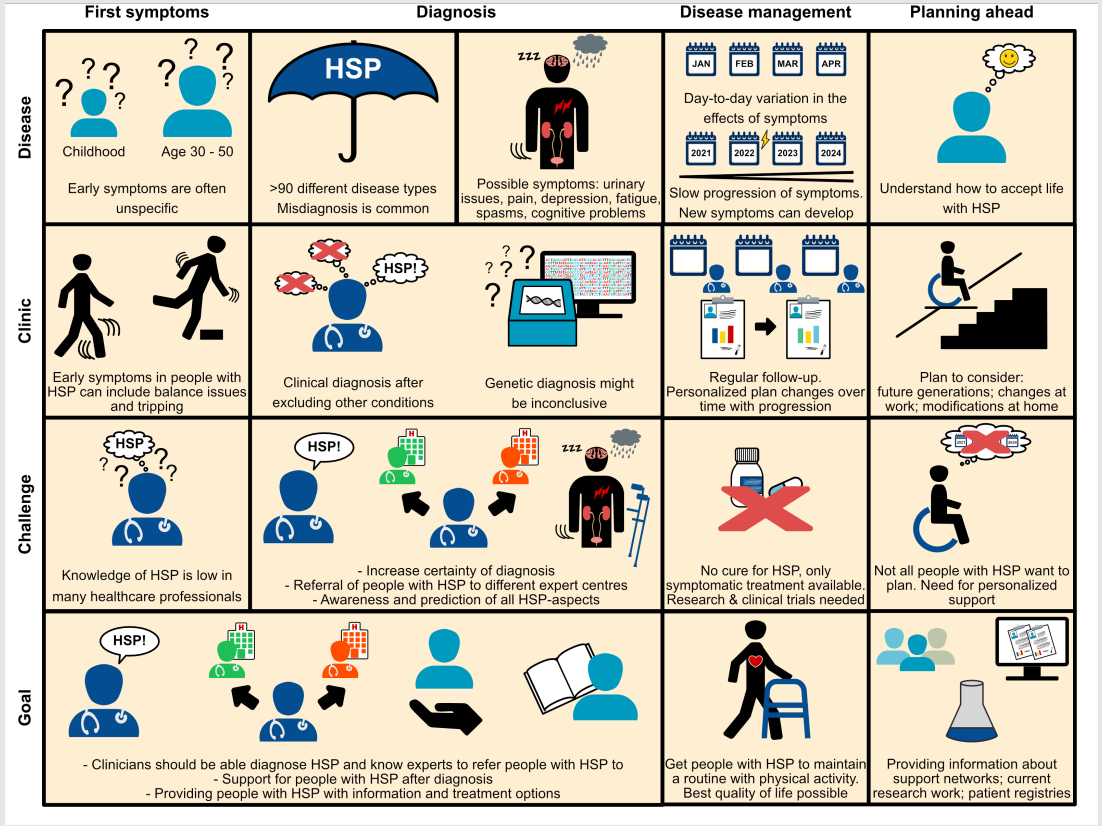
- Core activities of ERNs
  - Crossborder healthcare / CPMS

    > 3,450 cases
  - Training and education of health professionals

    Structured and sustainable training programs and curricula are being established
  - Patient journeys
  - ERN registry

    All ERNs, already >50,000 included patients
  - Guidelines and Clinical Decision Support Tools

    > 400 guidelines developed, appraised and endorsed




Example: Patient Journey for Hereditary Spastic Paraplegia

# Cross-Border Activities: ERNs as Intervention

**Aims**

- Improve healthcare of RD patients in EU
- Improve equity how healthcare is being provided for RD patients in EU

**Intervention activities**

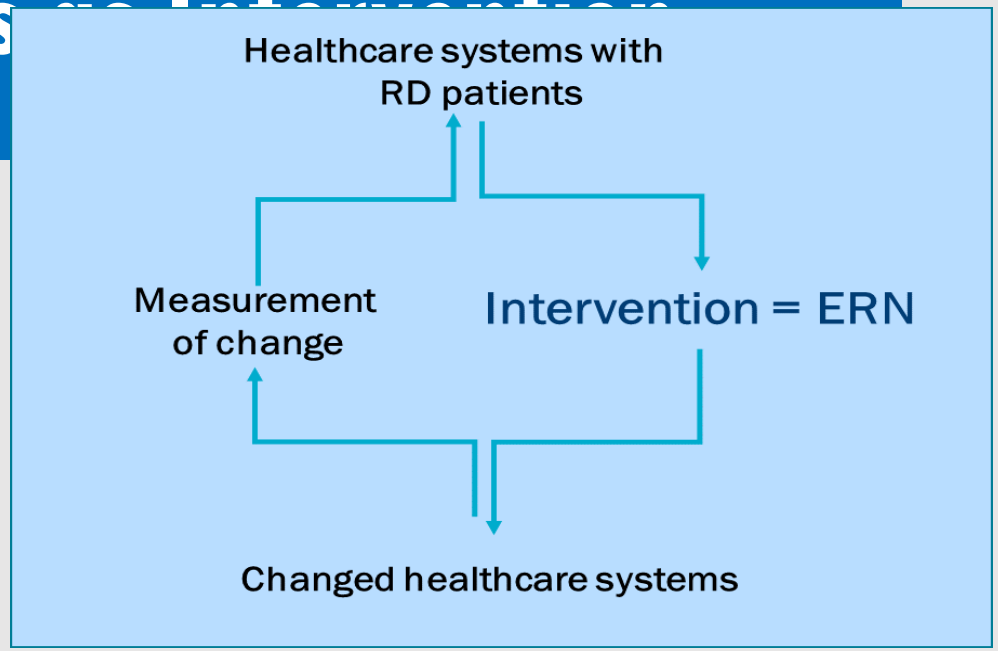
- Healthcare and CPMS
- Registries, data management and analysis
- Training and education
- Clinical Practice Guidelines and Clinical Decision Support Tools

**Typical procedure**

- Identify and analyse care inequality
- Design and implement intervention
- Measure change
- Adjust intervention

**Examples in ERN-RND**

- Quality of diagnostic NGS testing
- MLD treatment elegibility panel




**Main challenges**

- Integration of ERNs in national healthcare systems
- (Financial) sustainability

# Example 1: Quality of NGS testing in RND

## Quality assurance for the next-generation sequencing diagnostics of rare neurological diseases in the European Reference Network

Maver Aleš, Lohmann Katja, Borovečki Fran, Wolstenholme Nicola, Taylor Rachel L., Spielmann Malte, Tobias Haack, Gerberding Matthias, Peterlin Borut, Graessner Holm

European Reference Network | Neurological Diseases (ERN-RND)

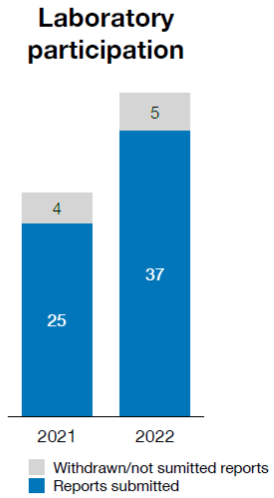
EAN conference 2022
Neurogenetics, Neuroepidemiology, & Neurological manifestation of systemic diseases 1
Saturday, 25 June 2022

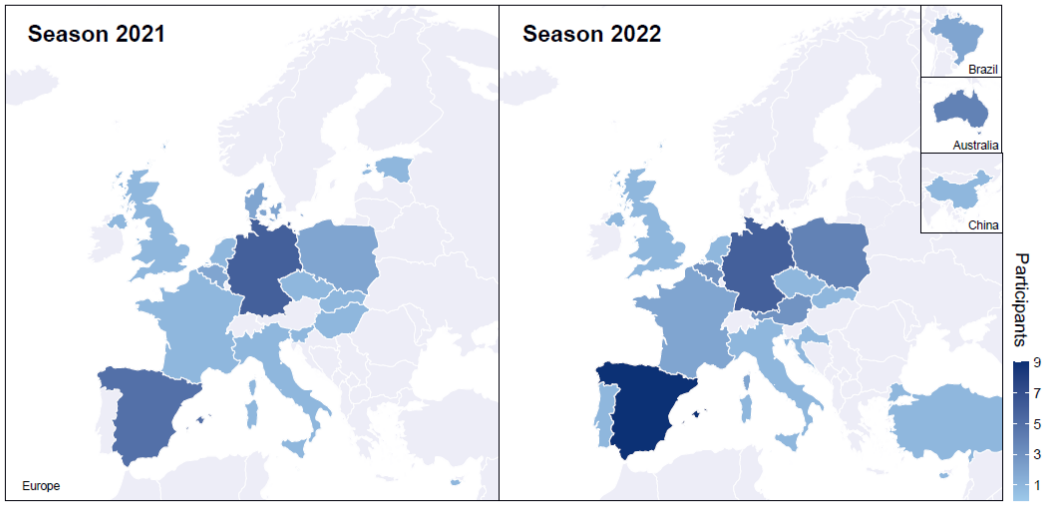
| Season | Case | Diagnosis | Validated result | Outcome |
|---|---|---|---|---|
| 2021 | 1 | **Familial Parkinson's disease** | Heterozygous for NM_198578.4:c.6055G>A p.(Gly2019Ser) | A pathogenic heterozygous variant confirming the presence of LRRK2-associated Parkinson disease |
| 2021 | 2 | **Spastic paraplegia** | Heterozygous for LRG_714t1:c.1291C>T p.(Arg431Ter) | A pathogenic heterozygous SPAST variant confirming the diagnosis of SPAST-associated spastic paraplegia |
| 2021 | 3 | **Amyotrophic lateral sclerosis** | No pathogenic variants identified | No molecular cause identified |
| 2022 | 1 | **Spastic paraplegia** | Hemizygous deletion of LRG_1017t1 (ABCD1) exons 6-10 | A pathogenic deletion in the ABCD1 gene, confirming a diagnosis of ABCD1-associated spastic paraplegia |
| 2022 | 2 | **Early-onset frontotemporal dementia with skeletal features** | Heterozygous for LRG_657t1(VCP):c.464G>A p.(Arg155His) | A pathogenic variant was identified in the VCP gene, confirming a diagnosis of Inclusion body myopathy with early-onset Paget disease and frontotemporal dementia 1 |
| 2022 | 3 | **Primary brain calcification disorder** | No pathogenic variants identified | No molecular cause identified |

# Quality of NGS testing in RND

## Participation in the scheme in the first two years

We received 28 applications in the pilot run. This increased to 42 in the second year.
Participations were from 17 and 18 distinct countries in the first and the second year, respectively.




Submissions from 17 countries

Submissions from 18 countries

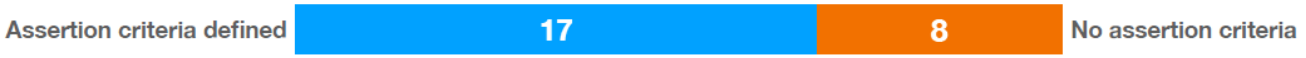
- Two finalised rounds
- 42 participating labs in 18 countries
- Majority of laboratories reported using either exome, clinical exome or genome sequencing
- A majority (70%) of labs reported using in-house developed pipelines for data analysis
- Of the participating laboratories, 7 laboratories (24.3%) did not report the pathogenic deletion, including two laboratories that declared using a CNV calling algorithm in the data analysis pipeline

# Quality of NGS testing in RND

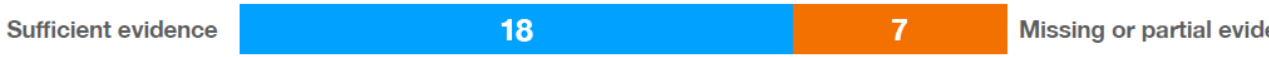
## Interpretation

A wider variability was observed in adherence to variant interpretation standards

- Several (32%) labs did not report using an accepted variant interpretation system




- 28% labs presented incomplete evidence to support variant's pathogenicity




- A minority of labs provided evidence codes supporting pathogenicity assertion


European Reference Network | Neurological Diseases (ERN-RND)

# Intervention

- Feedback to single labs and centres
- Development of expert opinion based recommendation for NGS testing in RND
- Guideline for NGS testing in RND

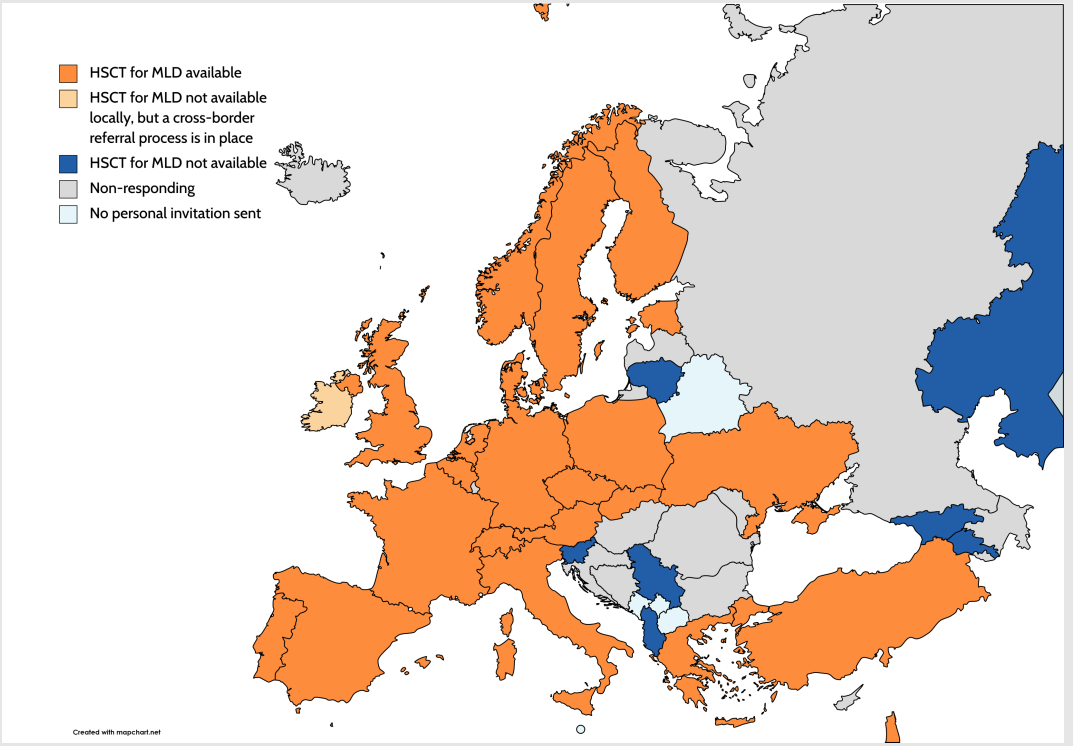
- Complemented by annual EQAs
  - NGS is topic of cross-ERN WG of Euro-NMD, RND and EpiCare
  - Euro-NMD is doing its first round of NGS EQA scheme

# Example 2 — MLD - hematopoietic stem cell transplantation

- HSCT for MLD is one of the highly specialized healthcare services of ERN-RND
- State of the art
  - HSCT for MLD is available in the majority of European countries uncertainties exist for many Eastern and South-Eastern European countries
  - Applied eligibility criteria are often not in line with the latest scientific insights

  → Care inequality

(Daphne H. Schoenmakers et al. Inventory of current practices regarding HSCT in metachromatic leukodystrophy in Europe and neighboring countries)



# Interv

- Cooperation of MLD initiative and ERN-RND
- MDT expert panel discusses MLD cases with regard to their treatment eligibility
- For EU clinicians and non EU clinicians
- Standardised workflow and forms
- Includes follow-up after treatment and by means of the MLD registry

## Treatment eligibility panel

Treatment with hematopoietic stem cell transplantation or gene therapy is only beneficial in early disease stages of MLD. Determining which patients might benefit from treatment and which do not, can be difficult. Therefore, an international MLD treatment eligibility expert panel can be consulted. When there is a need to discuss a case, the panel is convened on an ad hoc basis.

### When is discussion and advice by this panel recommended?

- Cases eligible for discussion include patients with a confirmed diagnosis of MLD for whom possible benefits of treatment with hematopoietic stem cell transplantation or gene therapy are not straightforward. Also presymptomatic cases can be discussed .
- All physicians in Europe are encouraged to discuss these cases with this panel.
- Also physicians from other geographical areas are invited to share and discuss their cases.

### Discuss a case

If you would like to discuss a case please contact the CPMS team and/or the MLD initiative.

- Physicians from EU countries can directly contact: cpms-helpdesk_ern-rnd@med.uni-tuebingen.de
- Physicians from non-EU countries should contact: MLDinitiative@amsterdamumc.nl

Before the meeting, the referring physician will be asked to complete a form with questions. Also, the patient should be informed and give informed consent. A digital meeting with international experts will be arranged. During the meeting, the referring physician briefly presents the case. A panel discussion will be held and an advice will be given. After the meeting, long-term follow-up will be ensured by including the patient in the MLDi registry.

**MLD treatment eligibility panel**

The panel discussions are completely aligned with and part of the CPMS case discussions of the ERN-RND.

More information about online case discussions with CPMS can be found here: https://www.ern-rnd.eu/cpms/

European Reference Network
for rare or low prevalence complex diseases
Network Neurological Diseases (ERN-RND)

**Are you a physician and do you want advice about an MLD patient?**

Contact us!

EU physicians: click here

non-EU physicians: click here

# Example – MLD - hematopoietic stem cell transplantation

Standard operating procedure

## MLD Treatment Eligibility Panel

The MLD initiative
ERN-RND

- Intervention:
  - Start March 2023

| | |
|---|---|
| Version | 1 |
| Status | approved |
| Date | 19-1-2023 |
| Purpose of this document | Describe the standard operating procedure for the panel discussing and advising on HSCT/GT eligibility in metachromatic leukodystrophy on individual case base. |

| Referring centre | Referring clinician | Date of discussion |
|---|---|---|
| University Hospital Leipzig, Germany | Caroline Bergner; Wolfgang Köhler | 13.03.2023 |
| University Hospital Leipzig, Germany | Caroline Bergner; Wolfgang Köhler | 13.03.2023 |
| University Hospital Leipzig, Germany | Caroline Bergner; Wolfgang Köhler | 13.03.2023 |
| University Medical centre Hamburg, Germany | Annette Bley | 13.03.2023 |
| APHP - Reference Centre for Leukodystrophies, Robert-Debré University Hospital, Paris, France | Caroline Sevin | 17.03.2023 |
| Finland Consortium: University Hospitals in Oulu, Tampere and Helsinki, Finland | Päivi Vieira; Johanna Uusimaa | 17.03.2023 |
| University Hospital Tübingen, Germany | Samuel Gröschel | 09.06.2023 |
| APHP - Reference Centre for Leukodystrophies, Robert-Debré University Hospital, Paris, France | Caroline Sevin | 09.06.2023 |
| San Raffaele Hospital, Milan, Italy | Francesca Fumagalli, Valeria Calbi | 09.06.2023 |

# Measurement

- ERN-RND registry
- MLD re

The MLD initiative (MLDi) is an international MLD registry and multi-stakeholder collaboration. The MLDi was initiated in 2020 by researchers from Amsterdam UMC. Currently, experts from 15 expert centers are involved. The MLDi closely collaborates with patient associations, regulatory authorities and drug developers.

**Our mission**

*To improve disease management of metachromatic leukodystrophy through an international disease registry and multi-stakeholder collaboration*

*One MLD registry with maximum impact*

# Scalability

- MLD treatment eligibility board as a blueprint for cross-border care pathways in ERN-RND:
  - Deep brain stimulation
  - Neuroradiology second opinion

- Genetic therapies is topic of cross-ERN WG of Euro-NMD, RND, EpiCare, Eye and MetabERN
  - Survey regarding access for genetic therapies in Europe is almost ready