

# The organization of the management of rare diseases in Europe and France

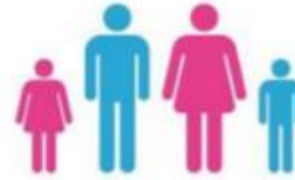
A Verloes



# Rare diseases in Europe

OVER  
**6000**  
distinct rare  
diseases

Each one affects  
fewer than  
**1 IN  
2000**  
PEOPLE



All together, an  
estimated

**30**  
MILLION PEOPLE  
are living with a rare  
disease in Europe



Expertise, knowledge,  
information on diseases and  
their consequences are **scarce**  
and **difficult to access**



**Rare, complex, chronic,**  
**disabling, progressive,**  
degenerative, often  
life-threatening

**NO  
CURE**   
for the vast  
majority of  
diseases and  
few treatments  
available

They are **geographically  
scattered** and often  
**isolated**

**Few experts,**  
geographically **scattered**  
**Research is fragmented**

# The complexity of rare disease landscape in EU

1.4 billion € for RD research in FP7 & Horizon 2020



ERDERA



février 24



RD Ref Centres in France and EU

869 patient organisations from 76 countries



European Commission



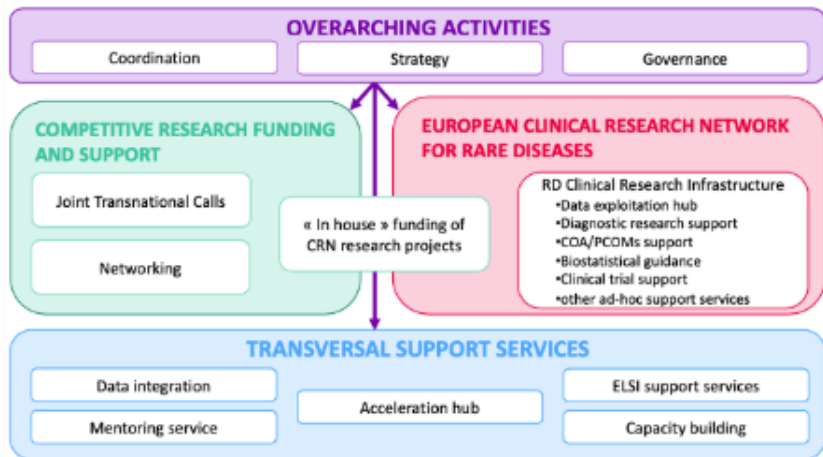
European Reference Networks



# Two EU initiative: care of RD (ERNs) & research on RD (ERDERA)



## European Rare Diseases Research Alliance



The RD Partnership implementation concept

### • EJPRD (European Joint Program on Rare Diseases)

- EJPRD : Part of the EU H2020 Work Programme (budget of €55 M for 5 years) (2019-2024)
- Consortium of 85 partners (29 research funding bodies/ministries and 5 charities/foundations, 12 research institutes + 33 universities & hospitals, 5 EU research infrastructures, EURORDIS & ePAGs)

### Replaced by **ERDERA** (under revision) : 2024-2031 - >150 M€

### • ERDERA's objectives

- **Improve the health** and well-being of the 30 million people in EU living with a rare disease (RD).
- Support the **prevention, diagnosis and treatment** of rare diseases.
- Commitment to the UN Sustainable Development Goals & Alignment with EU Policy Priorities

### • ERDERA's Vision

- **Structuring** the European Research Area on RD
- Leave no one behind by establishing a **multi-stakeholder ecosystem** for RD
- Supporting **patient-driven research**, developing new treatments and diagnostic pathways
- Using Health and Research **Data** for Digital Transformational Change in RD R&I
- **Coordinate and align national and regional research strategies.**
- Establishing **public-private** collaborations and maximising the EU's innovation potential in R&D.

### • ERDERA's missions

- Gather and share R&I knowledge, resources and services for RD research projects.
- Enable each consenting patient to participate in tailored **clinical studies** by generating and sharing regulatory-grade data.
- Make Europe a world leader in RD R&I by increasing investment to boost innovation.

# ERNS

- **European Reference Networks**

- **Origine**

- Directive 2011/24/UE : « *droits des patients en matière de soins de santé transfrontaliers* »

- **Objectives**

- Facilitate access to affordable diagnosis, treatment and high-quality care, including **across borders**
- Promote medical education, research, information dissemination, evaluation of care

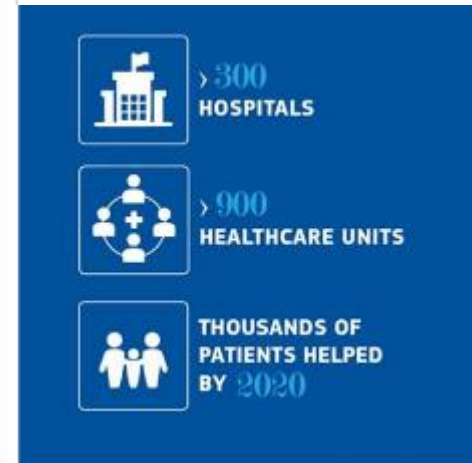
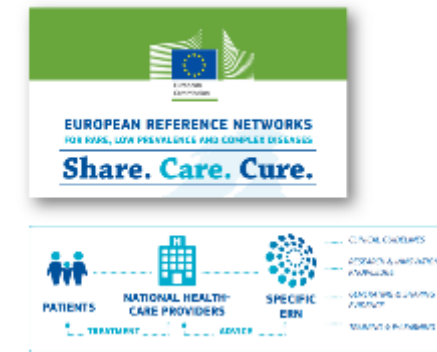
- **Creation**

- 15/12/2016: *Board of Member States*
- 01/03/2017: kick off
- 2022-23: renewal → September 30, 2027
- Unformal network of Hospitals endorsed by each Member State

- **Current landscape**

- 24 European Networks
- 20 ERNs: rare diseases in the strict sense
- 3 ERNs: rare cancers
- 1 ERN for childhood transplantation
- About 400 hospitals in 25 EU countries + Norway
- > 1600 centres of expertise, including 229 centres in France

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RD Ref Centres in France and EU

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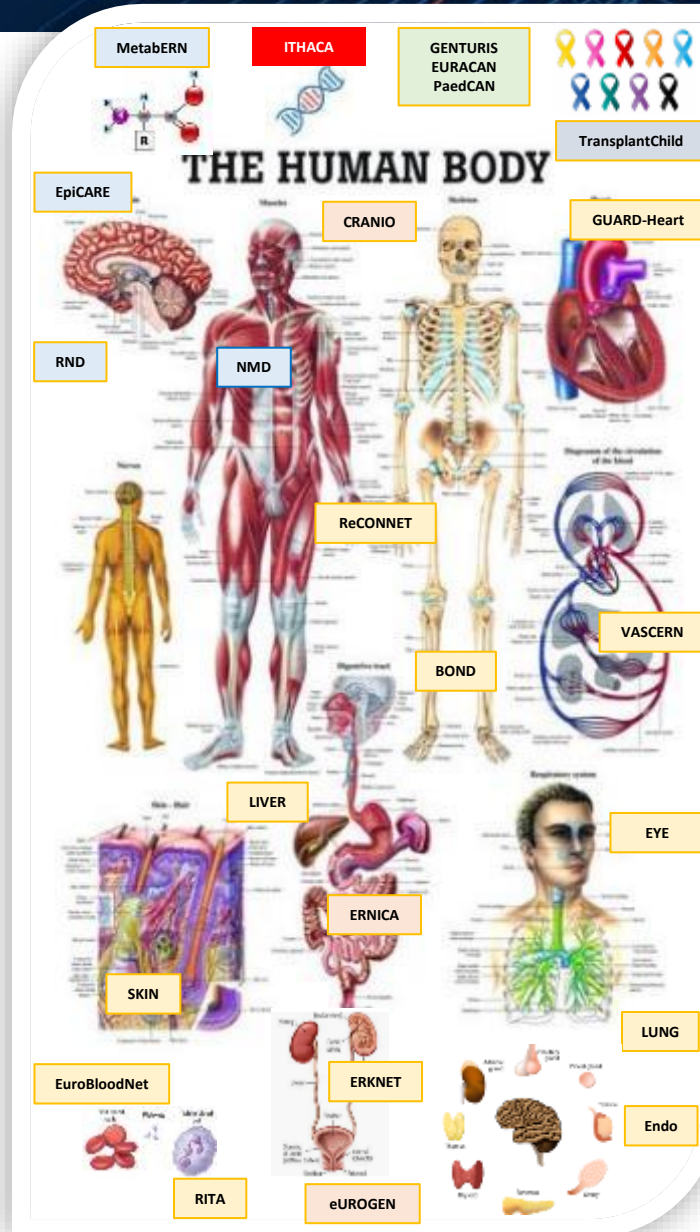
# 24 ERNs covering all aspects of rare/complex human diseases + rare cancers

## 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

# ERNs an inovative BUT complex approch to Health



## EUROPEAN REFERENCE NETWORKS

Helping patients with low-prevalence rare or complex diseases



European Reference Networks

Share. Care. Cure.

Health and Food Safety

- R = REFERENCE not RESEARCH
- Network of experts in rare/complex disorders
  - Working in national expert centres
  - Coordinated by a coordinator elected by its peers
- ERNs are not legal entities (not EU bodies/infrastructure)
- Based on a network of HCPs harbouring expert centres
  - Proposed by national authorities (no universal criteria)
  - NOT funded by EU for their involvement
  - The coordinating HCP is **funded for coordination** (ca 800 k€/Y) by EC
  - No co-funding requested by HCPs
- Linked to a dedicated Board of Member States
  - Variable interest to RD community
- « Subsidiary principle »
  - At least 27 Healthcare systems (regional OR national approach)
  - 27 research policies & medical cursus
  - Different access and refunding strategies for genetic tests
  - National RGPD constraints



## Intellectual disabilities, TeleHealth, Autism and Congenital Anomalies

- 2017: Coordinated by Manchester (Prof. Jill Clayton-Smith)
- 2019: Coordination transferred to Paris (post-Brexit)
- Network
  - 2017: 38 HCP
  - 2022: 71 HCP



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

### ERN on congenital malformations and rare intellectual disability (ERN ITHACA)

This ERN brings together experts in rare congenital malformations and rare intellectual disability disorders. Congenital malformations affect one in 40 babies. For more common malformations, such as cleft lip, there are well-established care networks. For rare conditions, expertise is scattered across the EU. Many malformations occur together as part of 'syndromes' associated with abnormal growth, development or social adaptation. Over 8 000 syndromes have been described, and most occur at a frequency of less than 1 in 2 000.

Chromosome disorders are one of the commonest causes of malformations and intellectual disability. New tests, such as exome and genome sequencing, have improved the prospects of diagnosis but are not routinely available in more than 50% of highly specialised centres.

Expanding access to this technology is a key goal of ERN ITHACA. The network is also developing telehealth initiatives with virtual multidisciplinary teams across EU centres, and will use virtual online clinics to improve access to diagnostics without requiring patients to travel.

ERN ITHACA will network parents and patients to develop best practice and initiate guideline development where required. It will establish criteria for patient registry data, advance training for health professionals and facilitate research. The network will work with existing networks in the field and with ERNs with whom there are complementary interests, while keeping patients at the centre of its activities.

**NETWORK COORDINATOR**  
Alain Verloes  
Assistance publique - Hôpitaux de Paris  
Hôpital Robert-Debré, Paris, France



## • Landscape

- Most HCPs are genetics departments in teaching hospitals

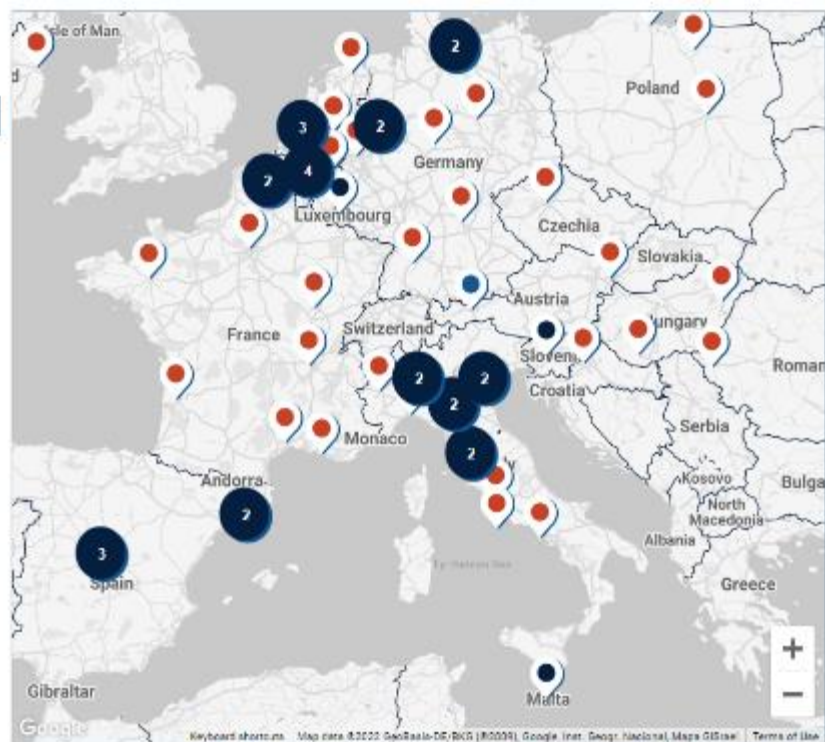


## • Scope

- Developmental abnormalities
  - Simple malformations and MCA
  - NDD (ID, ASD)
- Genetic, multifactorial (e.g. spina bifida) or environmental cause



# Intellectual disability, TeleHealth, Autism and Congenital Anomalies



## • History

- 2017-(2019)-2022 : ERN v1 (cofunding EU-HCP)
- 2022- 2023: ERN v2 bridge grant (100% EU funding)
- 1<sup>er</sup> Octobre 2023 - 30 Septembre 2027: ERN v2 final Grant
- **3 224 561 € (806 140 /an)**

## • Organization

- Multi-beneficiary
  - F: APHP RDB
  - NL: Amsterdam, Rotterdam, Groningen
  - I: OPBG
- Coordination team : 10 personnes
  - Paris : 3 PM + Anne (support financier : filière/APHP)
  - Groningen, Amsterdam, Rotterdam, Berne, Rome
- ExCom
  - coordination + WP leads

## • Board

- 71 HCP de 25+1 countries, including 3 hubs
- Related Structures: ERDERA (EJPRD+ Solve RD), Orphanet, IRdIRC, JARDIN

## • Non-EU affiliated partners (in progress)

- National Consortia : Switzerland, Turkey, Ukraine
- UK (Manchester, Others ? )
- **Extra European ??**



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RD Ref Centres in France and EU

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# Governance

## ERN Board

### Member state 1

HCP1-1  
Medical Team

HCP1-2  
Medical Team

...

Coord

Coord

### Member state 2

HCP2-1  
Medical Team

HCP2-2  
Medical Team

...

...

Coord

Coord

### Member state n

HCPn-1  
Medical Team

HCPn-2  
Medical Team

...

Coord

Coord

## Executive Committee

EJP-RD

1 invited rep

ERDERA

1 invited rep

Orphanet

1 invited rep

JARDIN

IRDIRC

1 invited rep

### Coordination team

#### ERN Coordinator

#### PM supporting WGs

- ERN PM
- PM Patient-oriented Actions & CPMS
- Communication Manager and Webmaster
- Pedagogical engineer - APOGeE
- Data Manager – ILIAD

- Methodologist CPGs and CDSTs (NL)
- Project Officer – CPGs and CDSTs (NL)
- Project Officer – NDDs (NL)
- Project Officer – Research (IT)
- IT developer (NL)
- DataManager – SysNDD (CH + DE)

WP1  
Coordination

WP2  
Dissemination

WP3  
Evaluation

WP4  
CPMS

WP5  
Registries

WP6  
T&E

WP7  
Guidelines

WP10  
Research & Pt

WP8  
Ukraine (1)

WP9  
Ukraine CPMS

WG1  
Coordination

WG2  
Dissemination

WG3  
Evaluation

WG4  
CPMS Healthcare

WG7  
ILIAD registry

WG8  
Teaching & Training

WG9  
APOGeE

WG11  
Expert Cons Statements

WG12  
Research & Innovation

WG5  
NeuroDev Disorders

WG chair + 1 co-chair  
→ ExCom

WG chair

Governance Of WGs

Co-chair 1

Co-chair 2

Co-chair 3

Co-chair n

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WG14  
Patient Adv Brd

WG15  
ELSI Adv Board

Task 1  
Task 2  
Task 3  
Task n

Task 1  
Task 2  
Task 3  
Task n

Task 1  
Task 2  
Task 3  
Task n

Task 1  
Task 2  
Task 3  
Task n

Task 1  
Task 2  
Task 3  
Task n

Task 1  
Task 2  
Task 3  
Task n

Task 1  
Task 2  
Task 3  
Task n

WG10  
EU Certif

Task 1  
Task 2  
Task 3  
Task n

WG6  
Fetal medicine

Task 1  
Task 2  
Task 3  
Task n

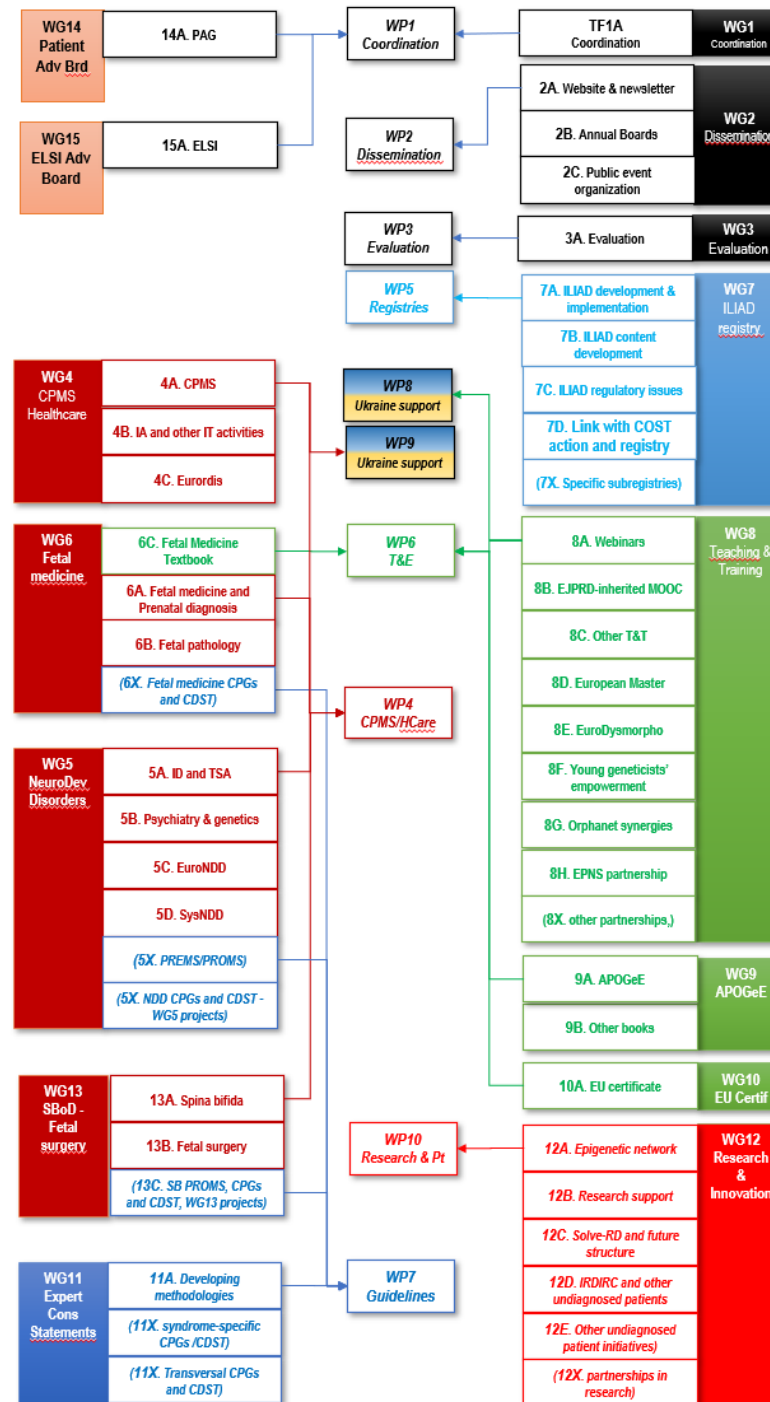
WG13  
SB -Fetal surgery

Task 1  
Task 2  
Task 3  
Task n

RD Ref Centres in France and EU

# WP, WG et Task Forces

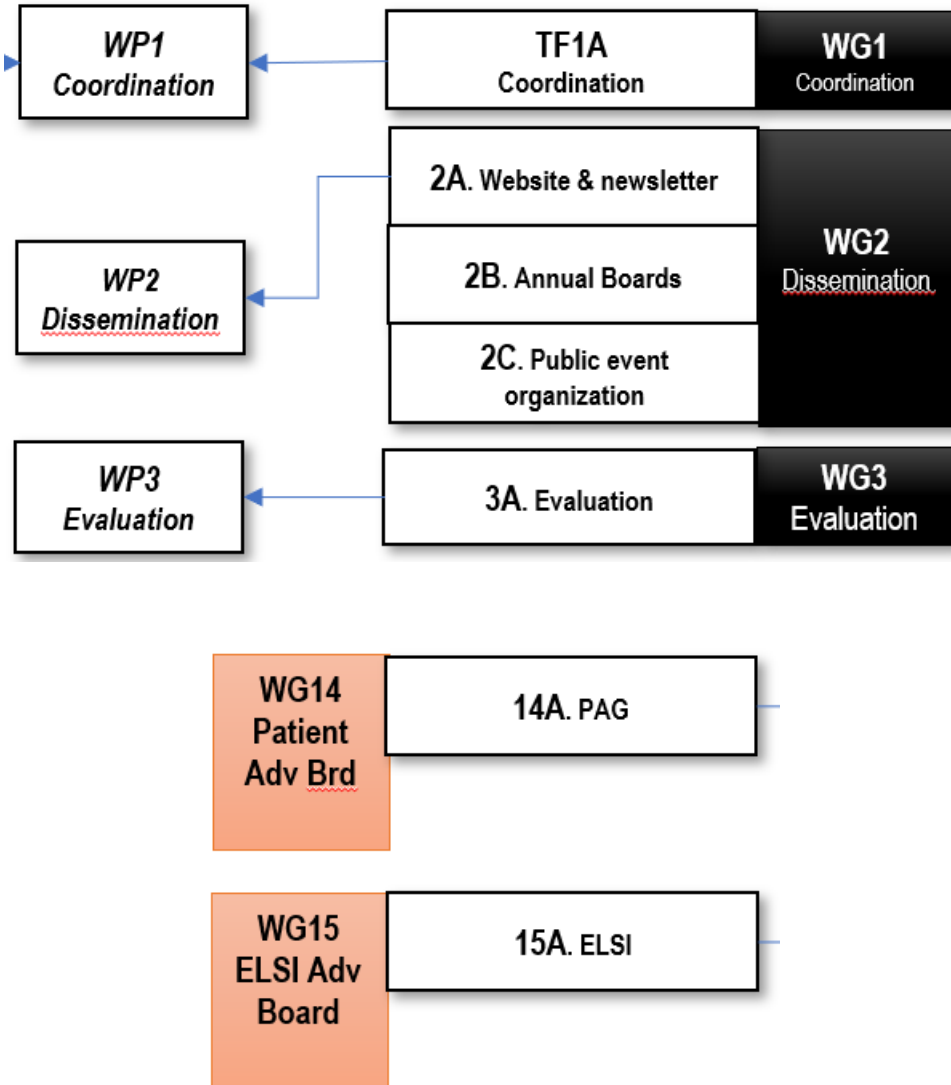
- 15 Working Groups consisting in :
- 39 permanent Task Forces
- + ~10 TF ad hoc
  - for specific thematic tasks (Guidelines, ITHACA sub-registers, PROMS))
- **Connexions**
  - ERDERA (European Rare Diseases Research Alliance) :
    - EU ResearchCoordination / MR
    - JARDIN: implementation of national RD networks in Europe
  - ERICA: Common regulatory documents



## New axes for 2023

- Fetal Surgery for Dysraphism
- Psychiatric manifestations of monogenic diseases
- Undiagnosed patients
- PROMS

# WP : general governance and advisory bodies



## • General coordination

- Boards & Excoms
- Support to events
- Website & NL
- Reporting

## • Relations with stakeholders & funding agencies

- DGSante (EC governance)
- HADEA (finance, EU level)
- APHP (finance, day-by-day)
- ERDERA

## • Patients advocacy groups

## • External ethical committee

# WP: clinical orientation

<b>WG6</b> Fetal medicine	<b>6C. Fetal Medicine Textbook</b>
	<b>6A. Fetal medicine and Prenatal diagnosis</b>
	<b>6B. Fetal pathology</b>
	<i>(6X. Fetal medicine CPGs and CDST)</i>

<b>WG5</b> NeuroDev Disorders	<b>5A. ID and TSA</b>
	<b>5B. Psychiatry &amp; genetics</b>
	<b>5C. EuroNDD</b>
	<b>5D. SysNDD</b>
	<i>(5X. PREMS/PROMS)</i>
	<i>(5X. NDD CPGs and CDST - WG5 projects)</i>

<b>WG13</b> SBoD - Fetal surgery	<b>13A. Spina bifida</b>
	<b>13B. Fetal surgery</b>
	<i>(13C. SB PROMS, CPGs and CDST, WG13 projects)</i>

## • Neurodevelopmental disorders

- Workshop
  - EuroNDD
- Web resource
  - SysNDD
- Guidelines (trans-WG)
- PROMS
- Psychiatric aspects

## • Developmental disorders

- Fetal medicine and PDg
- Fetal pathology
  - Winter course
- Dysraphisms (trans-ERN)
- Fetal surgery

# WP: experts & expertise

WG4 CPMS Healthcare	4A. CPMS
	4B. IA and other IT activities
	4C. Eurordis

WG11 Expert Cons Statements	11A. <i>Developing methodologies</i>
	(11X. <i>syndrome-specific CPGs /CDST</i> )
	(11X. <i>Transversal CPGs and CDST</i> )

- CPMS

- Expert statements

- Clinical Practice Guidelines (CPGs)
  - Syndrome specific
  - Problem specific
  - Transversal
- Clinical Decision Support Tools (CDST)
- Endorsement of existing CDST/CPG
  
- Methodology : AGREE II + Delphi

- PROMS

- With ERDERA

# WG : e-Education

8A. Webinars	WG8 Teaching & Training
8B. EJPRD-inherited MOOC	
8C. Other T&T	
8D. European Master	
8E. EuroDysmorpho	
8F. Young geneticists' empowerment	
8G. Orphanet synergies	
8H. EPNS partnership	
(8X. other partnerships,)	
9A. APOGeE	WG9 APOGeE
9B. Other books	
10A. EU certificate	WG10 EU Certif

- Webinars
- MOOCS
- APOgeE and other online teaching/learning material
- Support to EU UEMS certificate of genetics



# WG: research support

12A. Epigenetic network	WG12 Research & Innovation
12B. Research support	
12C. Solve-RD and future structure	
12D. IRDIRC and other undiagnosed patients	
12E. Other undiagnosed patient initiatives)	
(12X. partnerships in research)	

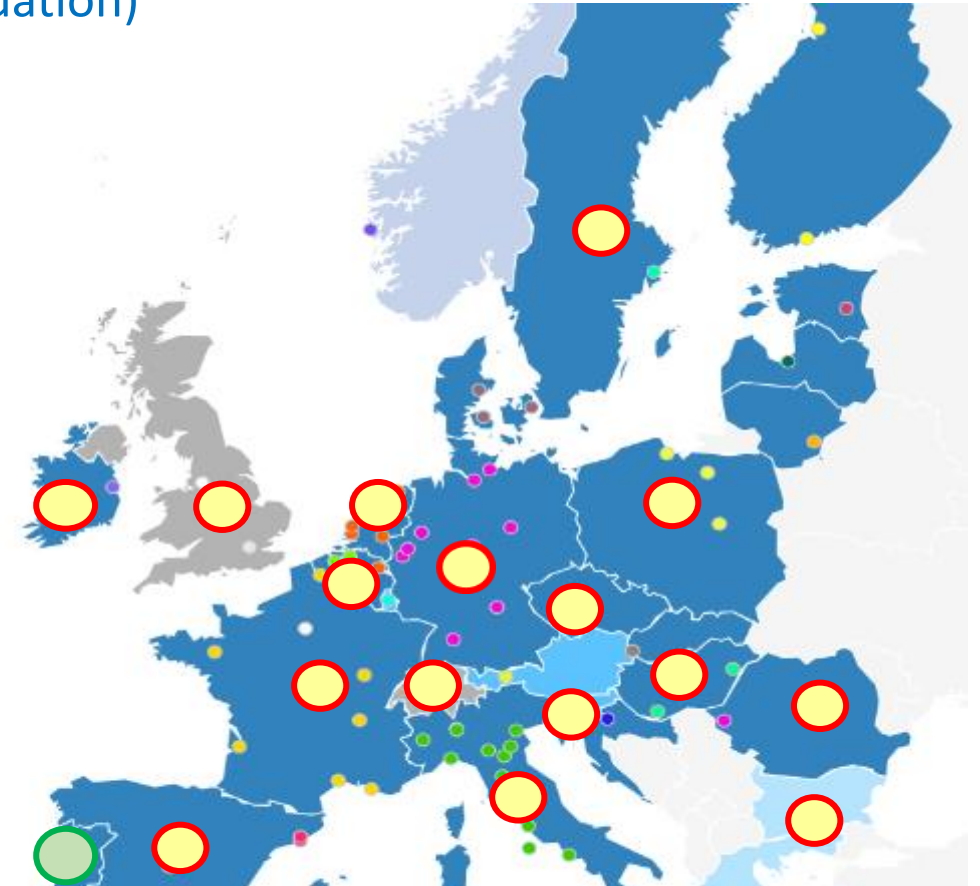
7A. ILIAD development & implementation	WG7 ILIAD registry
7B. ILIAD content development	
7C. ILIAD regulatory issues	
7D. Link with COST action and registry	
(7X. Specific subregistries)	

- Clinical research calls (series of patients)
  - Trough web site
  - Free access to the scientific community
- Short exchanges (with EJPRD)
- Contribution to Solve-RD and ERDERA
- Support to IRDiRC
- ILIAD registry
  - Core database on monogenic ID patients
  - Disorder-specific databases

# Une communauté de patients en pleine croissance - ePAGS (38 ePAGS + 30 PC)

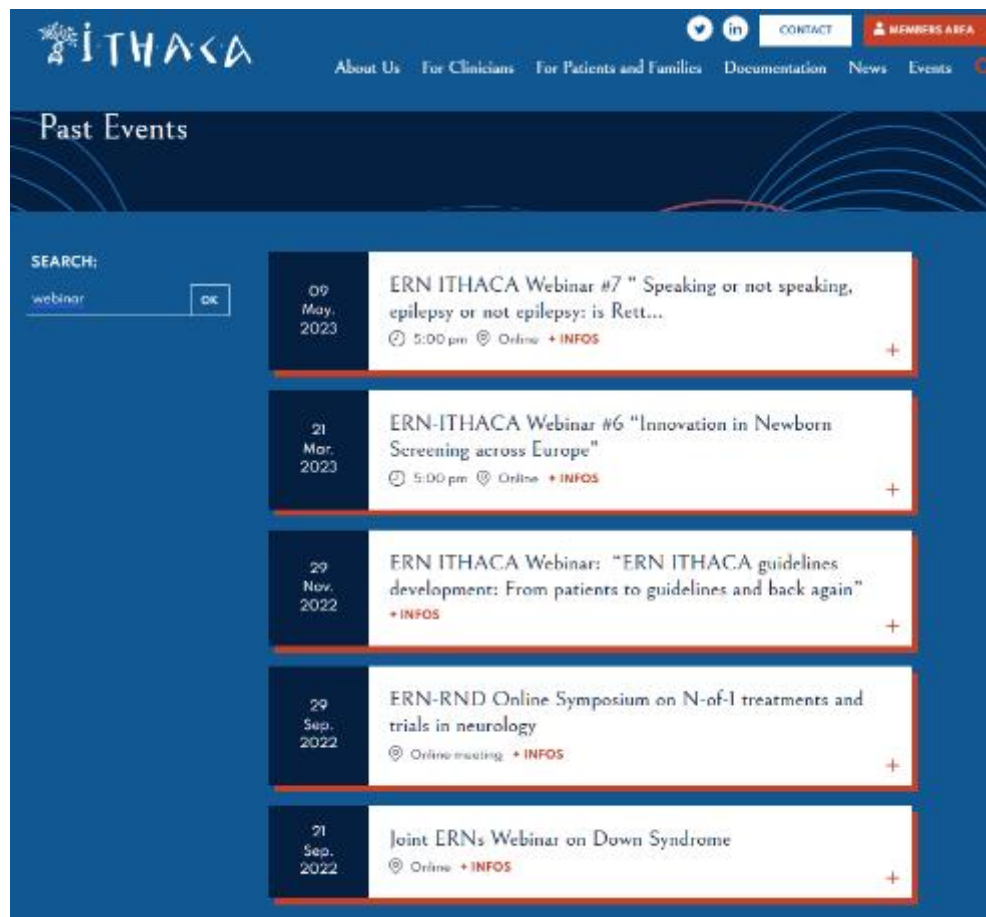
- Ouverture aux Assos sans diagnostic (SWAN, UDNI, Wilhelm Foundation)

22q11.2	Acrodysostosis	ADNP	Angelman	Beckwith-Wiedemann	Chromosomal disorders
Chromosomal abnormalities	Corpus Callosum	Costello and cardio-facio-cutaneous syndrome	Cowden (mental health)	Coffin-Lowry	Cdls Cornelia Delange
CDKL5	Dravet	Fragile X	Goldenhar	Kleefstra	MED13L
Mowat-Wilson	Noonan	PACS1	Pallister-Killian	Pitt Hopkins	Prader Willi
Phelan Mc Dermid	Rett	SAT2B	Smith-Lemli-Opitz	Smith-Magenis	Spina Bifida
Tuberous Sclerosis Complex	Williams	White-Sutton	Brain malformations, genetic on NDD	ID rare diseases	Ultra rare condition
	Undiagnoses no names	RD Borys the Hero Foundation	RD Alliance IT,ES,CZ,NL,FR,RO	Etc ..... Specific conditions	



Belgium (BE)	Greece (EL)	Lithuania (LT)	Portugal (PT)
Bulgaria (BG)	Spain (ES)	Luxembourg (LU)	Romania (RO)
Czechia (CZ)	France (FR)	Hungary (HU)	Slovenia (SI)
Denmark (DK)	Croatia (HR)	Malta (MT)	Slovakia (SK)
Germany (DE)	Italy (IT)	Netherlands (NL)	Finland (FI)
Estonia (EE)	Cyprus (CY)	Austria (AT)	Sweden (SE)
Ireland (IE)	Latvia (LV)	Poland (PL)	

# WG8: Teaching & Education - Webinars

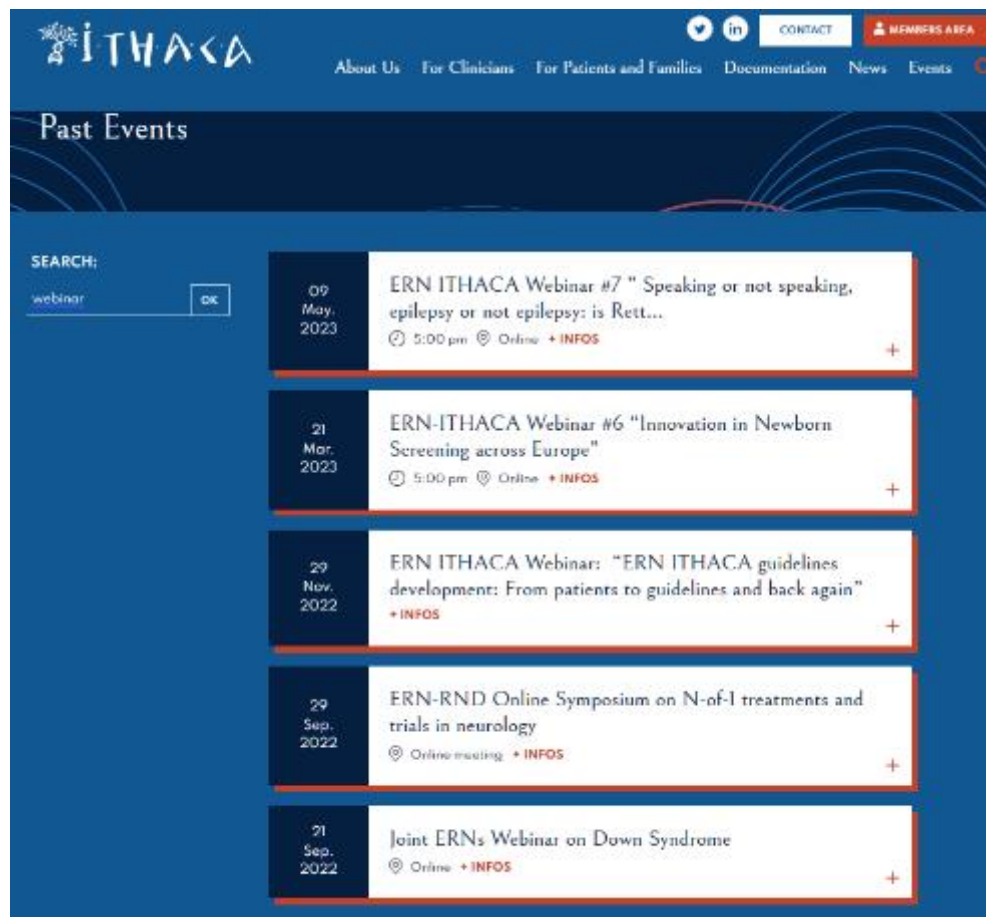


The screenshot shows the ERN ITHACA website's 'Past Events' section. A search bar on the left contains the word 'webinar'. The main content area displays a list of five webinars, each with a date, title, time, and format. The webinars are:

Date	Title	Time	Format
09 May 2023	ERN ITHACA Webinar #7 "Speaking or not speaking, epilepsy or not epilepsy: is Rett..."	5:00 pm	Online
21 Mar 2023	ERN-ITHACA Webinar #6 "Innovation in Newborn Screening across Europe"	5:00 pm	Online
29 Nov 2022	ERN ITHACA Webinar: "ERN ITHACA guidelines development: From patients to guidelines and back again"		
29 Sep 2022	ERN-RND Online Symposium on N-of-1 treatments and trials in neurology		Online meeting
21 Sep 2022	Joint ERNs Webinar on Down Syndrome		Online

- Coordination: Laurence FAIVRE (Dijon, FR) & Guiseppe ZAMPINO (Rome, IT)
- Easy support for e-learning
  - ZOOM, TEAMS...
  - Synchronous & interactive... OR not
  - Advertisement through ERN NL and Organizing partners
  - Usually opened to participants outside the Network
  - Further dissemination through dedicated ERN YouTube channel
- From some webinars to > 10/ERN/year
- **Common webinars with EPNS !!!**

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# WG8: Teaching & Education - Eurodysmorpho

- A 3-day workshop dedicated to developmental anomalies
  - > 80 oral presentation
  - 5 educational sessions
- Oriented to (and organized with) Young Geneticists and Young Child Neurologists

- 2024: Ljubliana
- 2025: Vilnius
- 2026: Italia



# WG8: Teaching & Education - MOOCs and other self-learning tools

- Asynchronous or synchronous (MOOCs) e-learning tools

- BIG

- Developped with Université Paris Cité
    - Second run in December 2023

- Diagnosing Rare Diseases: from the Clinic to Research and back

- Second run from October 4<sup>th</sup>

- EJPRD → ITHACA in Dec 2023
      - 5 224 enrolled on this course
      - 5 weeks - 3 hours per week
      - Digital certificate when eligible

- From focused information

- ...to large e-textbooks :

- ITHACA: APOGeE

Computer science and programming Health

## BIG - Introduction to Bioinformatics and Genomic Medicine

Ref. 37028

Duration: 5 weeks Effort: 15 hours Pace: Self paced

This follows the path of DNA sequencing in a medical context: from data generation to variants interpretation. It is set in the current context of the major development of genomic medicine.

Université de Paris

No open course runs



EJPRD - EUROPEAN JOINT PROGRAMME FOR RARE DISEASES

## LAUNCHES ITS FIRST FREE MOOC

DIAGNOSING RARE DISEASES: FROM THE CLINIC TO RESEARCH AND BACK

DURATION: 5 WEEKS

WEEKLY STUDY: 3 HOURS

100% ONLINE

EJPRDISEASES.ORG

# WG9: APOGeE

- Coordination: A Verloes + steering committee
- APOGeE
  - Online e-handbook on medical genetics
  - 100 contributors
  - Adopted as reference for **ECCMG certificate for Med Genetics** (UEMS)
  - With strong accent on NDD and developmental anomalies
  - In development (beta version)
  - Achievement T2, 2024

The screenshot shows the top navigation bar of the APOGeE website. It includes the ITHACA logo, navigation links for 'About Us', 'For Clinicians', 'For Patients and Families', 'Documentation', 'News', and 'Events', and buttons for 'CONTACT' and 'MEMBERS AREA'. Below the navigation bar, there is a banner for the 'Online Genetics Course APOGeE' and the APOGeE logo, which consists of the letters 'A.P.O.G.E.E' with a circular graphic between 'O' and 'G'. Below the logo is the text 'A Practical Online Genetics e-Education'.

This screenshot shows a page titled 'Noonan syndrome' with a 'Summary/outline' section. It includes a 'Clinical aspects' section with a 'Description and natural history' paragraph. Below the text are two photographs of a child's face, labeled 'A' and 'C', with anatomical labels in French. Label 'A' points to features like 'Grand front avec des tempes dilatées', 'Yeux écartés (ophtalmostrabisme)', 'Gonflement des paupières orientées vers le bas et le dehors', 'Arête nasale avec une pointe large', 'Philum bien marqué', and 'Lèvres charnues avec un V-Wildon'. Label 'B' points to 'Oreilles ovales, écartées, basculées en arrière' and 'Folds de peau dans le cou'. Label 'C' points to 'Cheveux bouclés épars', 'Grandes yeux bleus avec des paupières tombantes', 'Petit nez recourbé avec une pointe large', and 'Arc de cupidon marqué'.

ERN ITHACA - general presentat

This screenshot shows the course interface on a tablet. At the top, there is a navigation bar with 'My Modules' and 'This Module'. Below it, a 'Certificate of Completion' section is visible, followed by an 'Acknowledgments' section. A grid of course modules is displayed, including 'S1: Introduction to Human Genetics', 'S2: Genomics', 'S3: Variants and mutations', 'S4: Multifactorial/genetic predisposition to common diseases', 'S7: Clinical genetics and genetic Counseling', and 'S8: The genetics of developmental disorders'. A 'Table of contents' sidebar is open, showing the following structure:

- 1. Introduction to Medical Genetics
  - 1.1. What do geneticists do?
  - 1.2. Genetic diseases
  - 1.3. The heterogeneity of genetic diseases
- 2. Rare diseases
  - 2.1. Definition and prevalence
  - 2.2. Limited scientific understanding of RD
- 3. Impact of rare and genetic diseases
  - 3.1. Medical impact of rare and genetic diseases
  - 3.2. Societal impact of rare and genetic diseases
- 4. Patients without a diagnosis
  - 4.1. Diagnostic yield of genetic testing
  - 4.2. Diagnostic wandering

The main content area shows 'Chapter 1-1: The field of medical genetics: Genetic disorders, rare diseases, and orphan patients' by Alain Verloes, Eiko De Boer, and Sylvie Odent. A 'Next' button is visible at the bottom right.

# WG9 : other supports

## • Dysmorphology Vade Mecum

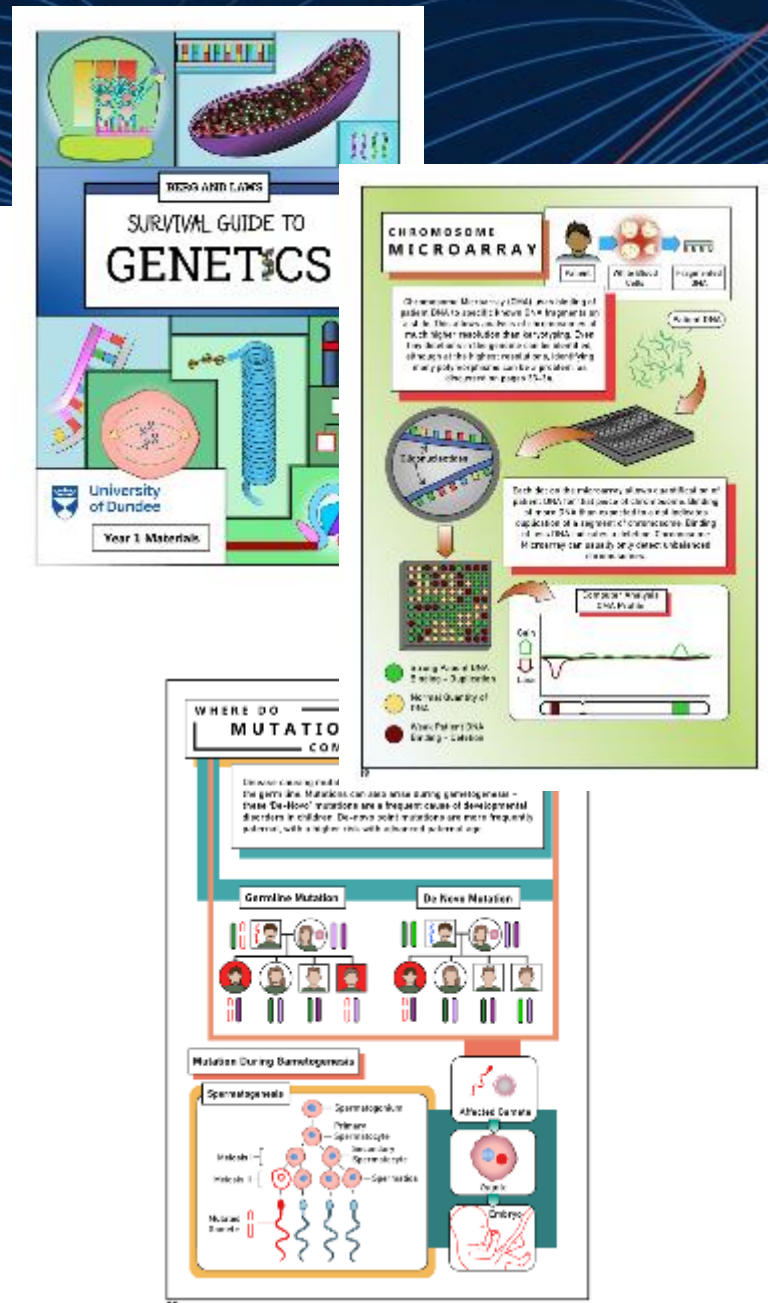
- Adaptation in GB of a French book (foreseen : mid 2024)

## • Genetic Survival Guide

- Small graphic book < Dundee University: VO online July 23
- To be adapted in several languages(FR to begin)
- Planned: "Genetic counseling" in the same format

## • Other projects

- Foetal pathology textbook?





# WG13: research support - Research calls

- Open to ITHACA and beyond
- Clinical research calls (series of patients)

SEARCH:  Keyword

Download here the template to submit your call by email to the coordination team

SORT BY:  
Newest  
A-Z (Gene/Syndrom)  
Deadline date

MTOR delineation and epesignature MTOR	+
SETD1A delineation and epesignature SETD1A	+
Further expansion of phenotypic spectrum of individuals with bi-allelic variants in CCDC82 CCDC82	+
Further delineation of SCAF4-associated NDDs	+
Fetal form of Tonne-Kalscheuer syndrome (TOKAS) associated with variants in RLIM Tonne-Kalscheuer syndrome	+

## Targeted gene under study

Smith-Kingsmore syndrome MTOR germinal (OMIM 616638 , ORPHA 457485)

## Abstract

Together with the Dijon team, we aim to better define the clinical, psychiatric and neuropsychological characteristics of people with germline MTOR variants, and to describe an epigenetic signature. We would be delighted to collect clinical data, neuropsychological, brain MRI, growth curves and a DNA sample. The Montpellier IRB is in the process of notifying us.

## Coordinating clinicians/researchers

David Genevieve - [d-genevieve@chu-montpellier.fr](mailto:d-genevieve@chu-montpellier.fr)

## Institution

Centre Hospitalier Universitaire de Montpellier, France

## Specific requirements beyond clinical data and genotype data sharing:

- Re-analysis of DNA samples: **No**
- Resampling of patients: **No**
- Linked to a translational/basic research project: **No**

- Thank you !



**[alain.verloes@aphp.fr](mailto:alain.verloes@aphp.fr) // [info@ern-ithaca.eu](mailto:info@ern-ithaca.eu)**

# RD in France : the 3 RD plans

## PNMR 1



2004

2008

**Create Centres (CR & CC)**  
RDs became a public health issue  
131 labelled RD Centres  
National RD Database

## PNMR 2



2011

2014 (16)

**Structure of RD Networks**  
Networks (*filières*)  
Rare Disease Foundation

## PNMR 3



2018

2022

**Consolidate**  
National RD database  
mandatory  
Undiagnosed patients

## PNMR 4

2024

2028

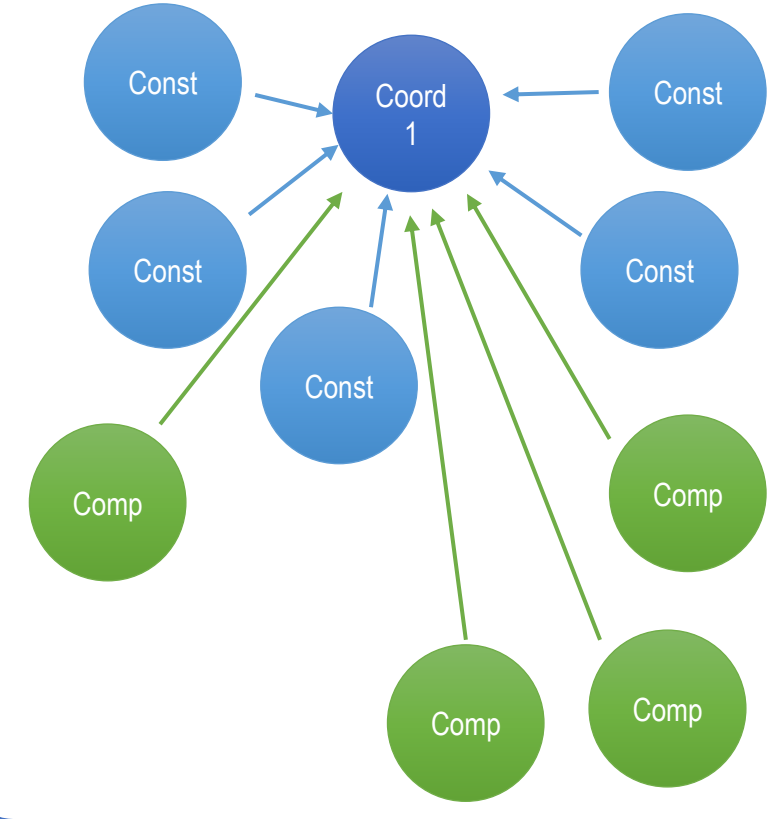
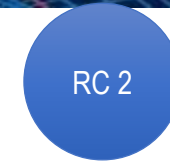
**Therapies**  
Health databases  
Bioinformatics  
?

# Concept of RD Reference Centres in France

- Holistic organisation for care and cure of rare diseases centered on Hospitals, encompassing local care and family support groups
- Basis: 3 levels
  - 1. Health network of Ref Ct (*Filière de Santé : FSMR*)
    - By broad medical area
    - 1 RC is FSMR coordinator
    - Encompass several Reference Centres
  - 2. Reference Centre (*CRMR*)
    - Monocentric : 1 coordinator
    - Multicentric : 1 coordinator + n constitutive
    - 1 or several in the same theme (depending on the prevalence)
  - 3. Competence centres (*CCMR*)
    - Affiliated with 1 RC
    - Regional mirrors > nation-wide coverage

FSMR

CRMR



# Basic criteria

- **Endorsement by Ministry of Health for 5 years**
  - Based on a medical project : structure and objectives
  - Evaluation by an independent Jury
- **Reference centre**
  - # of patients/Y (> 150) – declared through a national Registry
  - 1 or more by field (based on targetted population)
  - Active scientific activity
    - Publication (justified by bibliometry report)
    - PI in at least 1 funded research program (coordonnator or local PI)
  - Involvement in academic teaching
  - Supportive PAGs
- **Competence centre**
  - # patients/Y (> 25) – declared through registry
  - Geographic coverage complimentary to Ref
  - Active scientific activity

FSMR

CRM

RC 3

RC 4

RC 2

Const

Coord 1

Const

Const

Const

Const

Comp

Comp

Comp

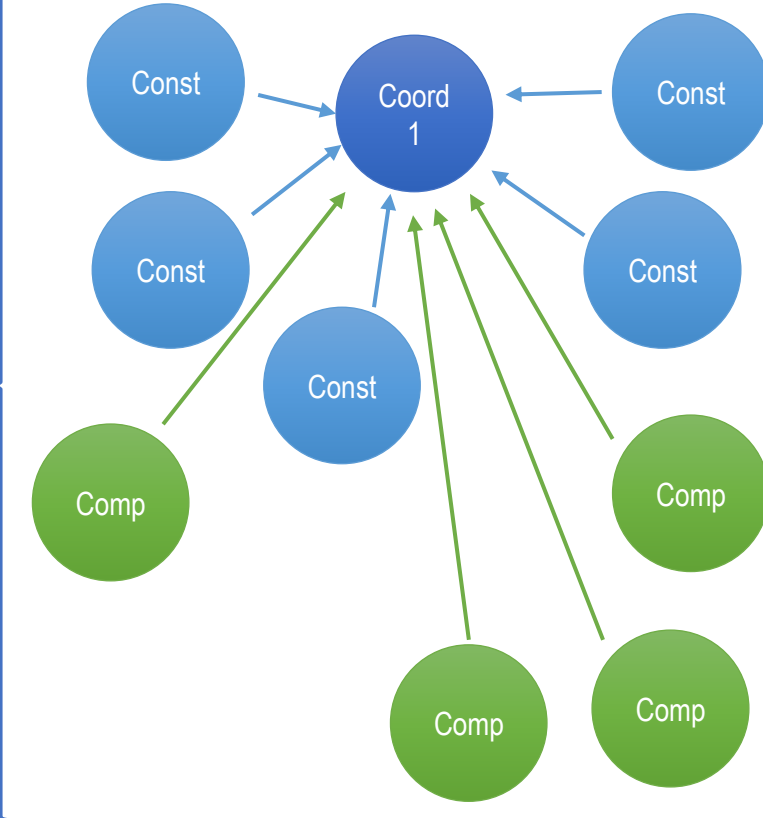
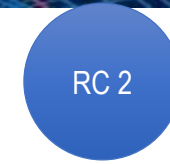
Comp

# Finance

- Closed envelope scattered among partners
  - 260 M/Y
- Health network
  - Coordination of several CRMR
  - FINANCING: for networking activities
- Reference centres
  - A fixed part / hospital + variable part based mainly on # of patients (250-400 k€)
  - Extra financing for the coordinating hospital (60 k€)
  - For non-medical staff and other actions (cannot be used to appoint MD)
  - Hospital overhead = 19% (or more: no commitment !!)
- Competence centre

FSMR

CRMR



# Monitoring

- Annual budget established for 5 years
- Annual monitoring
  - FSMR level
    - Activity report (annual)
  - CRMR level
    - Yearly on-line activity report
      - Active file as declared in BaMaRa (justified)
      - + scientific production, teaching, guideline...
      - Hospital impact

FSMR

CRMR

RC 3

RC 4

RC 2

Const

Coord  
1

Const

Const

Const

Const

Comp

Comp

Comp

Comp

# RD reference Centres: 5 aims

- **Coordination**

- Identifies, **coordinates** and animates its partners (medical, medicosocial, medico-educative)
- **Integrates PAGs** into the centre's activities and involves them in the definition of its objectives
- All CRMR actions in coordination with the general objectives of its **FSMR**

- **Expertise**

- Multidisciplinary synthesis or consultation meetings (consensus meetings)
- Produces National Diagnostic and Care Protocols (**PNDS**)
- Regular epidemiological records (All patients recorded in the National Rare Diseases DataBank **BNDMR**)

- **Remediation**

- Ensures multidisciplinary, diagnostic, therapeutic and follow-up care
- Depending on the case, CRMR provides this comprehensive care or organizes it within caregivers

- **Research**

- Promotes, animates or participates in translational, clinical, or organizational research.

- **Education and training**

- University, postgraduate and other teaching in the field of the group of RDs
- Therapeutic Education



# Filières

## 23 Filières

- |                                                                                                                                                                                                             |                                                                                                                                                                                    |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  <p>ANDDI-Rares<br/>Anomalies du développement déficience intellectuelle de causes rares</p>                               |  <p>FILFOIE<br/>Maladies hépatiques rares de l'enfant et de l'adulte</p>                          |
|  <p>BRAIN-TEAM<br/>Maladies rares à expression motrice ou cognitive du système nerveux central</p>                         |  <p>FILSLAN<br/>Sclérose latérale amyotrophique et maladies du neurone moteur</p>                 |
|  <p>cardiogen<br/>Maladies cardiaques héréditaires</p>                                                                     |  <p>imrad<br/>Maladies rares en dermatologie</p>                                                  |
|  <p>DéficitScience<br/>Maladies rares du développement cérébral et déficience intellectuelle</p>                           |  <p>FIRENDO<br/>Maladies rares endocriniennes</p>                                                 |
|  <p>AIPR illore<br/>Maladies auto-immunes et auto-inflammatoires systémiques rares</p>                                     |  <p>FIMATHO<br/>Malformations abdomino-thoraciques</p>                                            |
|  <p>FAVA-MULTI<br/>Maladies vasculaires rares avec atteinte multi-systémique</p>                                           |  <p>EM<br/>Maladies héréditaires du métabolisme</p>                                               |
|  <p>Filnemus<br/>Maladies rares neuromusculaires</p>                                                                       |  <p>MaRIH<br/>Maladies rares immuno-hématologiques</p>                                            |
|  <p>ORKID<br/>Maladies rénales rares</p>                                                                                   |  <p>RespiFIL<br/>Maladies respiratoires rares</p>                                                 |
|  <p>MCGRE<br/>Maladies constitutionnelles rares du globule rouge et de l'érythropoïèse</p>                                 |  <p>SENSGENE<br/>Maladies rares sensorielles</p>                                                  |
|  <p>MHEMO<br/>Maladies hémorragiques constitutionnelles</p>                                                               |  <p>FILIERE SANTE MALADIES RARES TeteCou<br/>Maladies rares de la tête, du cou et des dents</p> |
|  <p>Filière MUCO CFTR<br/>Mucoviscidose et affections liées à une anomalie de CFTR</p>                                   |                                                                                                                                                                                    |
|  <p>NeuroSphinx<br/>Complications neurologiques et sphinctériennes des malformations pelviennes et médullaires rares</p> |                                                                                                                                                                                    |
|  <p>OSCAR<br/>Os-Calcium/Cartilage-Rein</p>                                                                              |                                                                                                                                                                                    |

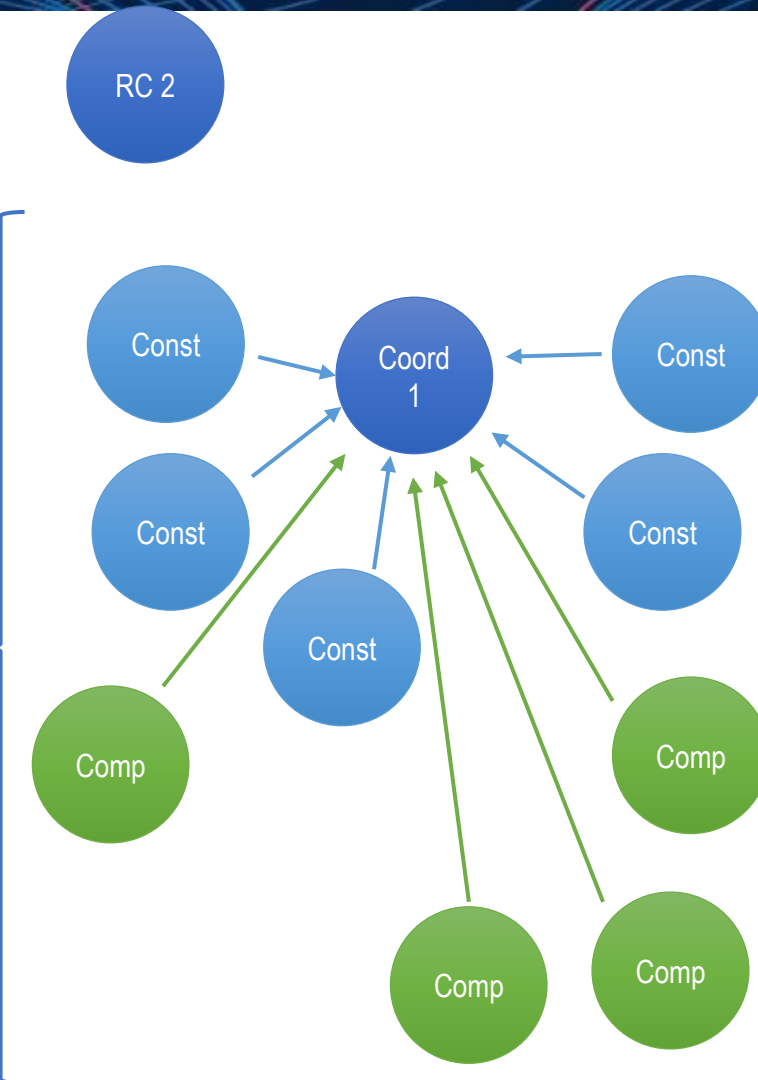
FSMR

CRMR

RC 3

RC 4

RC 2



# Filières

## 23 Filières



## Aims

- promote the legibility of the organization of the RD care to facilitate the orientation of patients and professionals
- decompartmentalize (social, medico-social, social)
- Missions
- Improving the care of people with RD
  - The FSMR reinforce, pool and coordinate all actions to improve overall management and the dissemination of expertise and knowledge.
  - The FSMRs do not organise the individual care of patients, which remains the responsibility of the CRMRs attached to them.
- Implementation of translational, clinical and organizational research
  - Support function
- Development of training and information
  - FSMRs identify and support educational programs
  - Information for FSMR stakeholders and outside the FSMR

# Centre mapping



Centres experts  
et filières /  
réseaux

Centres experts  
Filières / Réseaux

Cartographie des  
filières

Réseaux de référence  
européens

Accueil > Centres experts et filières / réseaux > **Cartographie des filières**

## Cartographie des filières

Le Ministère de la Santé a labellisé 23 Filières de Santé Maladies Rares afin d'améliorer la coordination des structures concernées par un ensemble cohérent de maladies rares. Chaque filière regroupe des Centres de Référence Maladies Rares (CRMR) qui peuvent être mono-site et ce site unique est « site coordonnateur » ou multi-sites avec un « site coordonnateur » et un ou plusieurs « sites constitutifs » complémentaires. Le pilotage des filières est assuré par un « animateur » désigné en son sein.

Toutes régions

Toutes les Filières

Centres Experts

Tous les types de centres



Site compétence

Site coordonnateur

★ Animateur filière

# National Protocol for Diagnosis and Care

The screenshot displays the HAS website interface. At the top, the HAS logo is on the left, and the tagline 'Développer la qualité dans le champ sanitaire, social et médico-social' is on the right. A search bar is located in the top right corner. Below the header, a navigation menu includes 'La HAS', 'Évaluation & Recommandation', 'Accréditation & Certification', 'Outils, Guides & Méthodes', and 'Social & Médico-social'. The main content area is titled 'Protocoles nationaux de diagnostic et de soins (PNDS)'. It features a search box for PNDS by title, a filter for 'Ancienneté' (Age) with options for 'Moins de 5 ans' and 'Plus de 5 ans', and a table of publications. The table lists various syndromes and conditions with their corresponding PNDS status. On the right side, there are sections for 'Abonnez-vous à l'actualité de la HAS', 'Le Webzine de la HAS', 'Vos interlocuteurs', and 'Bonne pratique - Dernières publications'. A video player is also visible at the bottom right.

**Recherche** > Avancée  
Saisir vos mots clés

La HAS | Évaluation & Recommandation | Accréditation & Certification | Outils, Guides & Méthodes | Social & Médico-social

Accueil > Évaluation & Recommandation > Bonne pratique professionnelle > Protocoles Nationaux de Diagnostic et de Soins

Recherchez par maladie

Devenez Expert auprès de la HAS  
La HAS recherche des experts pour ses groupes de travail

La HAS

- Commission des stratégies de prise en charge
- Commission des pratiques et des parcours
- Méthodes d'élaboration des recommandations de bonne pratique
- Méthode d'élaboration des Protocoles nationaux de diagnostic et de soins (PNDS)

Accréditation & Certification

- Mieux connaître l'accréditation
- Site de l'accréditation des médecins
- Productions et enseignements
- Chiffres-clés

Outils, Guides & Méthodes

- Développement Professionnel Continu (DPC)
- Protocoles pour professionnels
- Éducation Thérapeutique du patient
- Examen classant National

Protocoles nationaux de diagnostic et de soins (PNDS)

La production de protocoles nationaux de diagnostic et de soins (PNDS) par les experts des centres de référence maladies rares a été prévue initialement dans le premier plan national maladies rares 2005-2008 et a été confirmée dans le deuxième plan national maladies rares 2011-2014 à l'aide d'une méthode proposée par la Haute Autorité de Santé (HAS).

L'objectif d'un PNDS est d'expliquer aux professionnels concernés la prise en charge diagnostique et thérapeutique optimale actuelle et le parcours de soins d'un patient atteint d'une maladie rare donnée. Il a pour but d'optimiser et d'harmoniser la prise en charge et le suivi de la maladie rare sur l'ensemble du territoire.

Le PNDS peut servir de référentiel au médecin traitant (médecin désigné par le patient auprès de la Caisse d'assurance maladie) en concertation avec le médecin spécialiste notamment au moment d'établir le protocole de soins conjointement avec le médecin conseil et le patient, dans le cas d'une demande d'exportation du ticket modérateur au titre d'une affection très rare.

Les synthèses destinées au médecin généraliste traitant sont disponibles sur [une page spécifique](#).

La HAS se réserve le droit de procéder à un [audit](#) de la qualité méthodologique de quelques PNDS.

PNDS élaborés par les centres de référence

Rechercher un PNDS par son titre :

Ancienneté

- Moins de 5 ans
- Plus de 5 ans

Titre de la publication	Typ..
Syndromes FOXG1 et « FOXG1 plus »	PNDS
Phénylcétonurie	PNDS
Hypophosphatémies héréditaires à FGF23 élevé (dont hypophosphatémies liées à l'x)	PNDS
Syndrome de Marfan et apparentés	PNDS
Syndrome d'Ondine	PNDS
Dyskinésies ciliaires primitives	PNDS
Maladie de Rendu-Osler	PNDS
Insensibilités aux androgènes	PNDS
Syndrome de Cohen	PNDS

Abonnez-vous à l'actualité de la HAS

Le Webzine de la HAS

Vos interlocuteurs

Service des bonnes pratiques professionnelles  
Nous contacter

Bonne pratique - Dernières publications

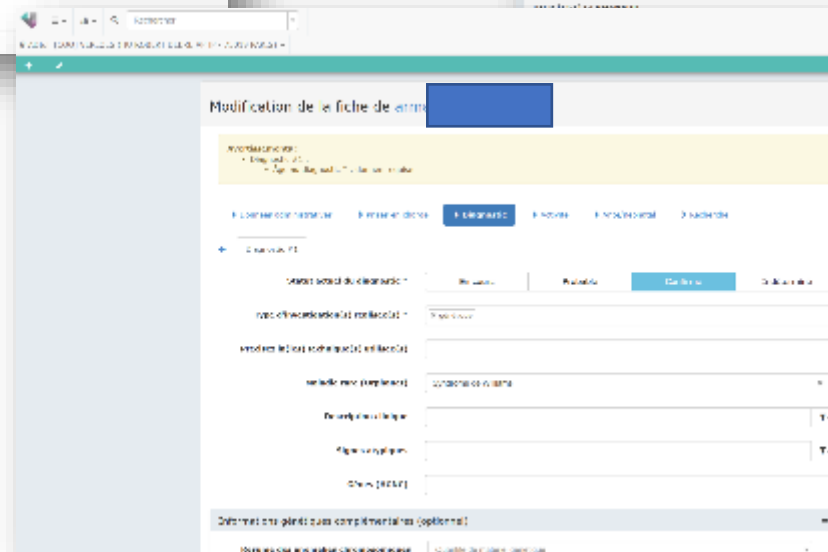
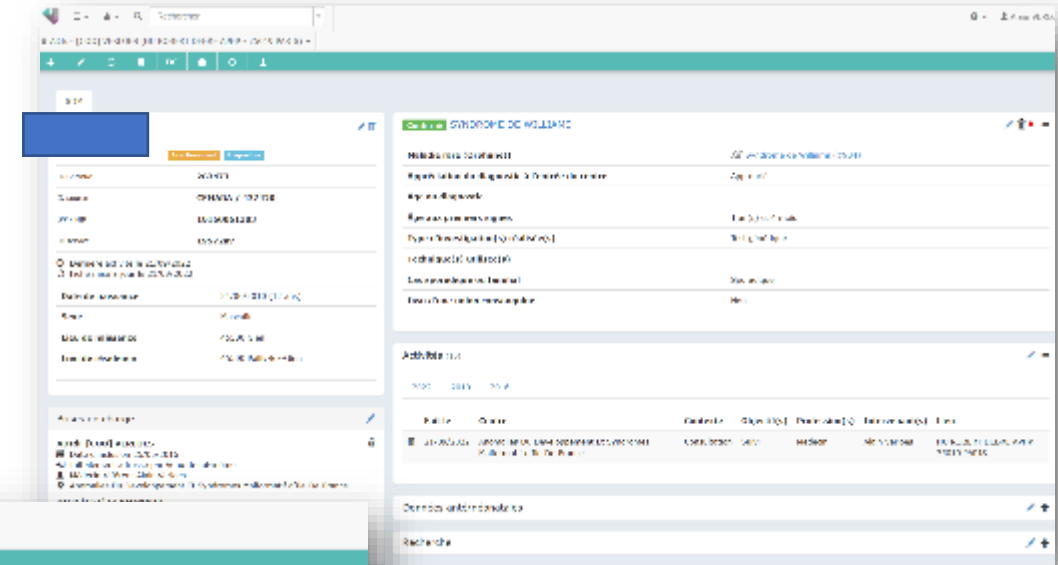
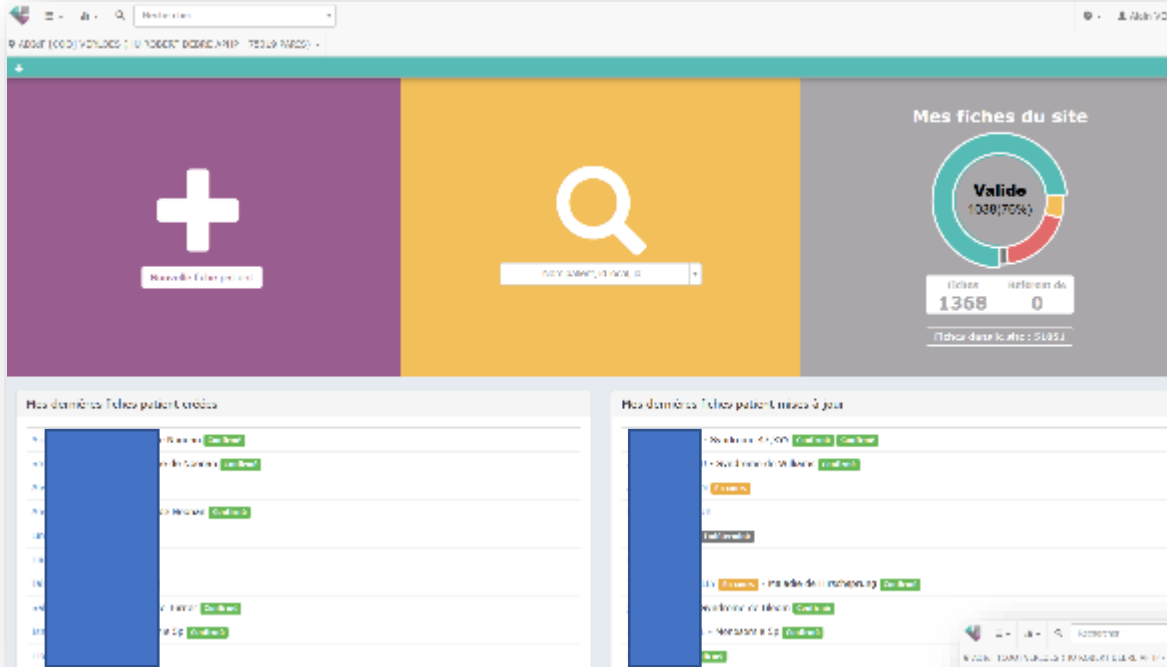
- Syndromes FOXG1 et « FOXG1 plus »
- Maladies bulveuses auto-immunes / Pempfigus
- Hypophosphatémies héréditaires à FGF23 élevé (dont hypophosphatémies liées à l'x)
- Aide à la rédaction des certificats et avis médicaux dans le cadre des soins psychiatriques sans consentement d'une personne majeure à l'issue de la période d'observation de 72 heures
- Contraception œstroprogestative transdermique ou vaginale : dispensation en officine
- Contraception chez l'adolescente

VIDÉO

Pourquoi le trouble bipolaire est-il difficile à diagnostiquer ?  
13/02/2015

HAS Pourquoi le trou...  
S'ABONNER 1 €...

# BaMaRa & BNDMR: diagnosis & activity registry



- 1 single nat.l database for all CRMR
  - 1 identifiable DB/hospital (BaMaRa)
  - → 1 unique anonymized Health Data Warehouse (BNDMR)
- More than 1.000.000 patients entered since 2007
- IT partitioning by site and CRMR
- Incorporated in IT system of most academic hospitals

février 20

# Filières vs ERNs



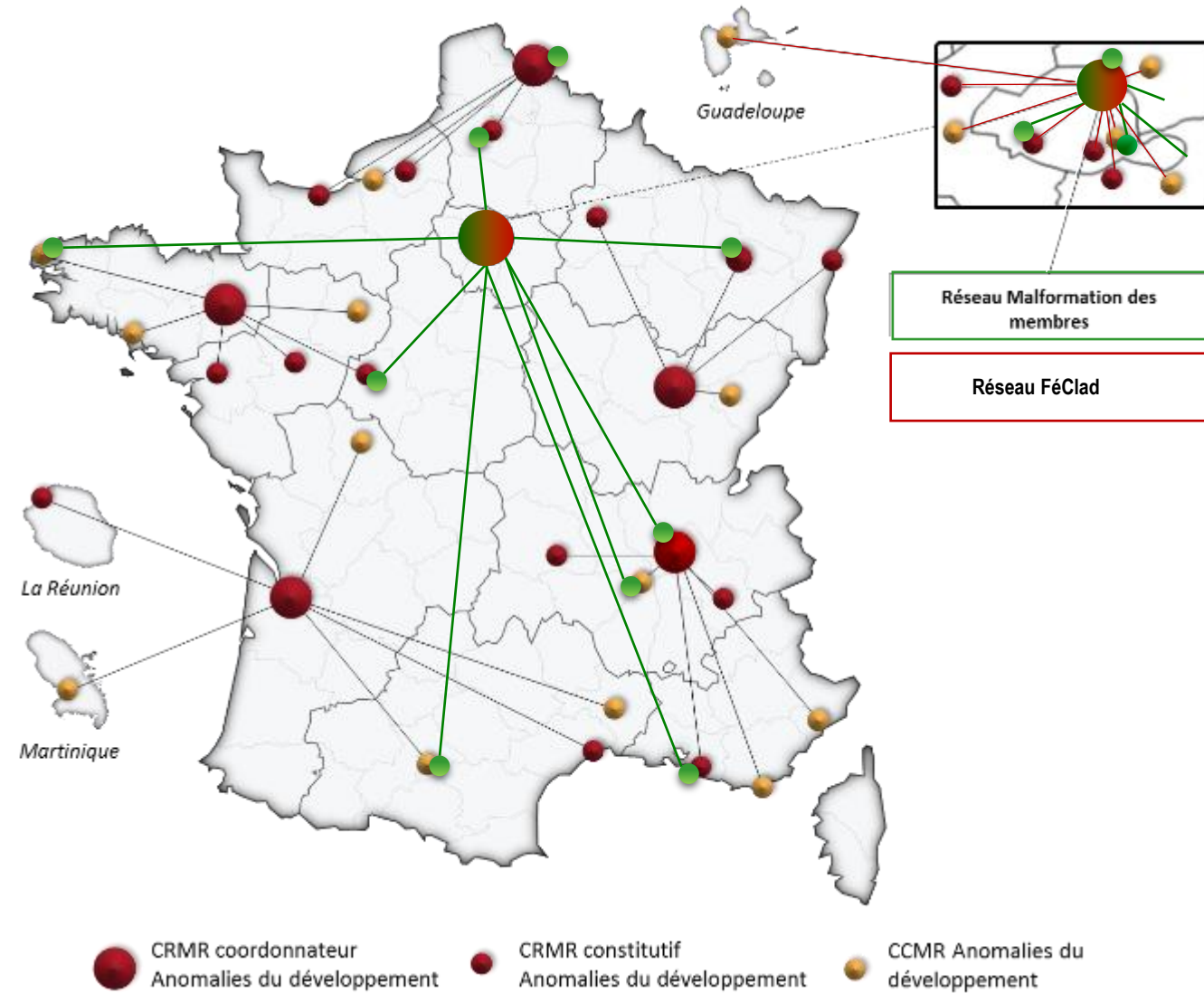
MINISTÈRE  
DES AFFAIRES SOCIALES  
ET DE LA SANTÉ

DIRECTION  
GÉNÉRALE  
DE L'OFFRE  
DE SOINS

## CORRESPONDANCES FSMR/ ERN

	ERN	FSMR
1	<b>Craniofacial Anomalies and ENT Disorders</b> (Congenital anomalies of the skull and face, including hearing disorders and upper airway anomalies)	TETE COU - SENSGEN
2	<b>ENDO ERN</b> (Rare Endocrine Diseases)	FIRENDO
3	<b>EpiCARE</b> (Rare and Complex Epilepsies)	DEFISCIENCE
4	<b>ERN EYE</b> (Rare Eye Diseases)	<b>SENSGEN</b>
5	<b>ERN SKIN</b> (Rare and Undiagnosed Skin Disorders )	<b>FIMARAD</b>
6	<b>ERNICA</b> (Rare inherited and congenital digestive disorders, including rare gastrointestinal diseases)	FIMATHO
7	<b>eUROGEN</b> (European Reference Network in Rare and Complex Uro-recto-genital Diseases and Conditions)	NEUROSPHINX
8	<b>EuroBloodNet</b> (Rare Haematological Diseases, y compris maladies malignes)	<b>MARIH – MCGRE- MHEMO</b>
9	<b>ITHACA</b> (Intellectual disability TeleHealth And Congenital Anomalies) Rare Congenital Malformations and Developmental Anomalies and Rare Intellectual Disability	ANDDI - DEFISCIENCE
10	<b>ERN LUNG</b> (Rare Respiratory Diseases)	RESPIFIL - MUCO/CFTR
11	<b>MetabERN</b> (Rare hereditary metabolic disorders)	G2M
12	<b>ERN RND</b> (Rare Neurological Diseases)	BRAIN TEAM
13	<b>ERN BOND</b> (Rare Bone Diseases)	OSCAR
14	<b>GUARD-HEART</b> (Rare diseases of the heart)	CARDIOGEN
15	<b>EURO-NMD</b> (Rare Neuromuscular Diseases)	FILNEMUS FILSLAN
16	<b>RITA</b> (Rare Immunodeficiency, Autoinflammatory and Autoimmune Network)	FAIIR
17	<b>RECONNET</b> (Rare Connective and Musculoskeletal Diseases)	FAIIR
18	<b>RARE-LIVER</b> (Rare hepatological diseases)	FILFOIE
19	<b>VASCern</b> (Rare Multisystemic Vascular Diseases)	<b>FAVA-Multi</b>
20	<b>ERKN</b> (Rare kidney diseases)	ORKID
21	<b>TRANSCHILD</b> (Transplantation in children incl. HSCT, heart, kidney, liver, intestinal, lung and multiorgans)	Aucune
22	<b>GENITURIS</b> (Genetic Tumour Risk Syndromes)	Aucune
23	<b>PaedCan ERN</b> (European Reference Network on Paediatric Cancer)	Aucune
24	<b>EUROCAN</b> (Rare Adult Cancers)	Aucune

# Le réseau de soin AnDDI-Rares



**36 CRMR + 57 CCMR = 93 centres**

- AD: 24 CRMR + 21 CCMR = **45 centres** (+9 sites)
- CeRefAM: 3 CRMR + 12 CCMR = **15 centres** (+1 site)
- GenoPsy: 5 CRMR + 6 CCMR = **11 centres** (nouveau)
- Spin@: 3 CRMR + 10 CCMR = **13 centres** (nouveau)
- PaRaDiGM: 1 CRMR + 8 CCMR = **9 centres** (nouveau)

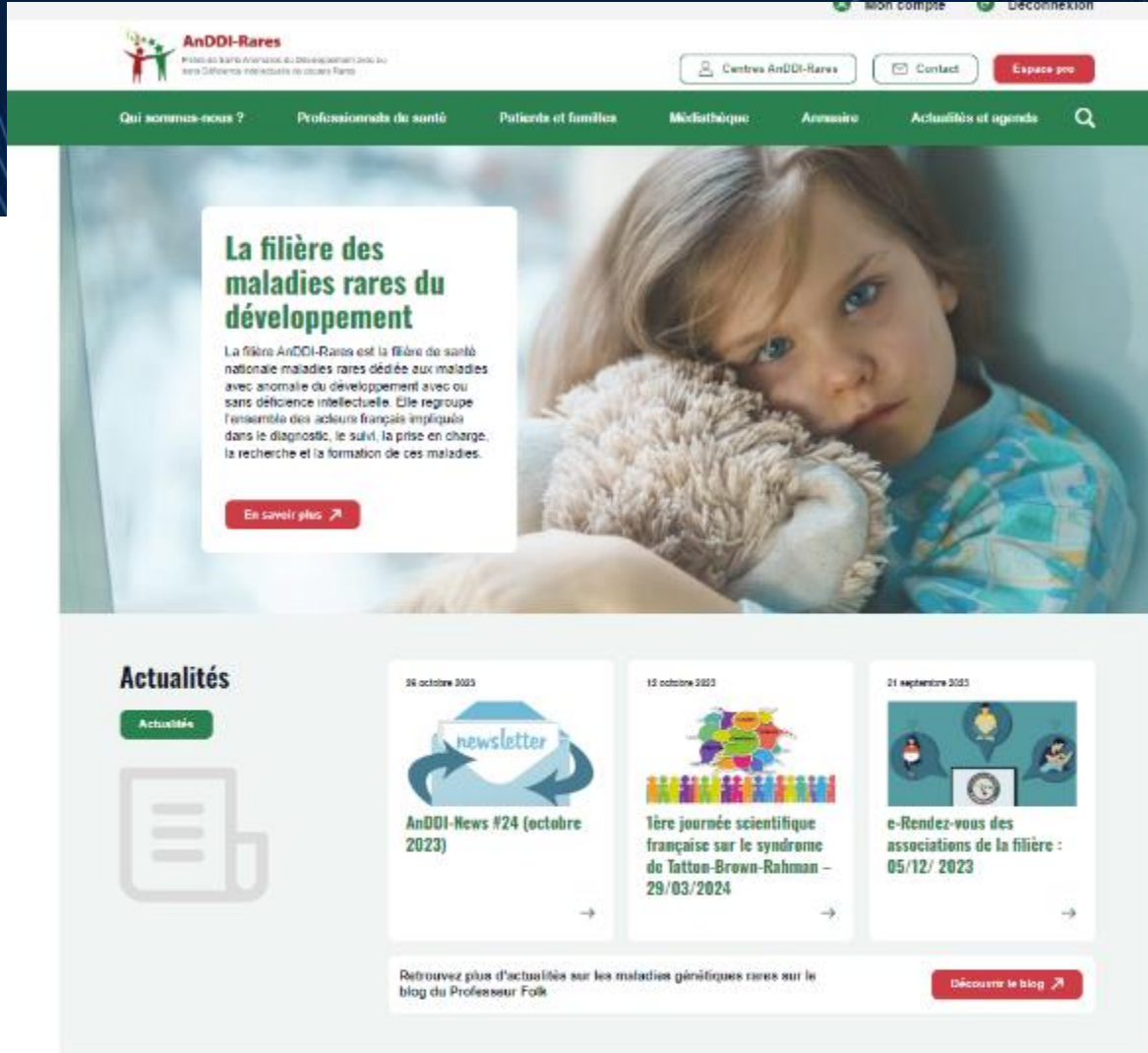
+169%



# Site Web

-  Diagnostic et PEC
-  Expertise pluridisciplinaire
-  Communication
-  Recommandations
-  BNDMR
-  Recherche
-  Médico-social
-  Formation
-  Europe
-  Associations
-  Interfilière
-  SoFFoet

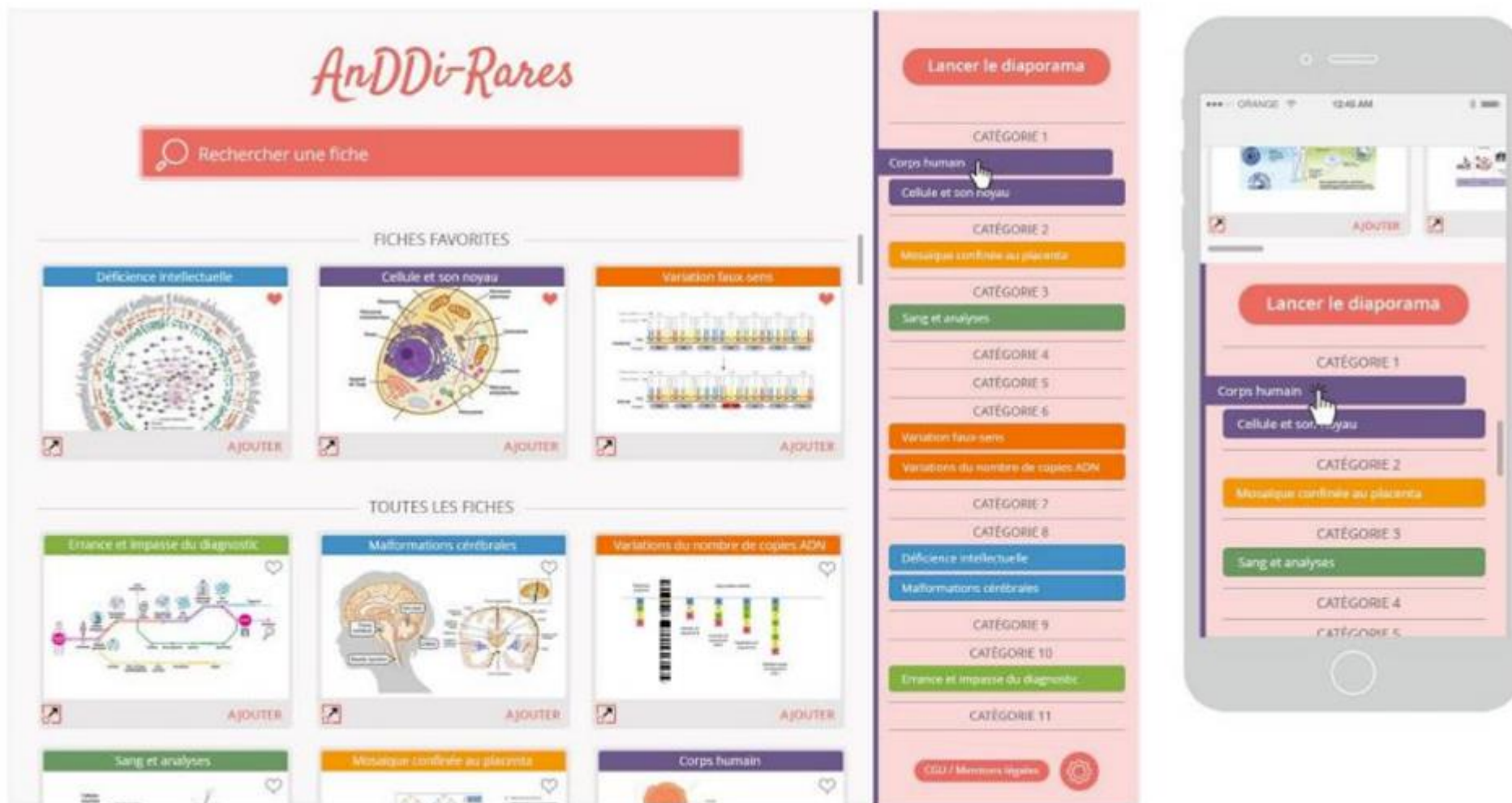
février 24



The screenshot shows the homepage of the AnDDI-Rares website. At the top, there is a navigation bar with the AnDDI-Rares logo and menu items: 'Centres AnDDI-Rares', 'Contact', and 'Espace pro'. Below the navigation bar is a main banner with a photograph of a young child holding a stuffed animal. The banner features the title 'La filière des maladies rares du développement' and a brief description of the organization's mission. A 'En savoir plus' button is located at the bottom of the banner. Below the banner is an 'Actualités' section with three news items: 'AnDDI-News #24 (octobre 2023)', 'Tère journée scientifique française sur le syndrome de Tatton-Brown-Rahman - 29/03/2024', and 'e-Rendez-vous des associations de la filière : 05/12/ 2023'. A 'Découvrez le blog' button is at the bottom right of the news section.







The image displays the AnDDi-Rares application interface. On the left, a desktop view shows the main menu with a search bar, a 'FICHES FAVORITES' section with three cards (Déficience intellectuelle, Cellule et son noyau, Variation faux sens), and a 'TOUTES LES FICHES' section with three cards (Entrée et impasse du diagnostic, Malformations cérébrales, Variations du nombre de copies ADN). On the right, a vertical sidebar lists 11 categories from 'CATÉGORIE 1' to 'CATÉGORIE 11'. A 'Lancer le diaporama' button is visible at the top of the sidebar. On the far right, a mobile phone screen shows the same interface adapted for a smaller screen, with the 'Lancer le diaporama' button and category list clearly visible.

# Collaboration between ITHACA/French subsidiaries and African countries

- On the Web

- Webinars
- Free downloadable teaching material
- ITHACA Calls for Collaboration
- Treatment Protocols
  - French sectors
  - European sectors
- MOOC BIG
- Access to French inter-university diplomas supported by the course (dysmorphology, personalized medicine, etc.)
- EuroDysmorpho

- Co-development?

- Francophone : AnDDI-Rares / ITHACA (as an EU-Africa collaboration)
- English Speaking : ITHACA

Thank you for your attention !

